THE LONGEVITY EVIDENCE SERIES • BOOK THREE

OUTRUNNING ALZHEIMER'S

What a Global Longevity Community Tested—and What the Evidence Now Says About Protecting Your Brain



MARK A. SMITH

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Research, drafting, figures, and cover art were produced with AI assistance under the author's direction; every source cited was checked against the original, and any errors are the author's.

The Longevity Evidence Series, Book Three.

For Deborah Hall, and everyone else on the thread.

A note on medicine and evidence

This is a work of reporting and scientific interpretation, not medical advice. It documents public discussion of prescription drugs, supplements, peptides, devices, tests, and self-experiments on the forum rapamycin.news, and it sets that discussion against the published evidence. It does not diagnose, prescribe, or replace individualized care, and reading it does not create a clinician–patient relationship with the author or the publisher. Inclusion of a drug, supplement, test, or practice does not mean endorsement.

No intervention in these pages has been established as a way to prevent Alzheimer's disease. As of October 2026, no drug or supplement is approved to prevent Alzheimer's disease or dementia in people without symptoms. The anti-amyloid antibodies lecanemab (Leqembi) and donanemab (Kisunla) are approved only for early symptomatic Alzheimer's disease with confirmed amyloid, and their labels carry boxed warnings about amyloid-related imaging abnormalities (brain swelling and bleeding). Sirolimus (rapamycin) is a prescription immunosuppressant approved for specific uses, such as preventing kidney-transplant rejection, and its label carries a boxed warning about immunosuppression, serious infection, and malignancy. Metformin, SGLT2 inhibitors, GLP-1 drugs such as semaglutide, maraviroc, telmisartan, bumetanide, lithium carbonate, valacyclovir, and testosterone are prescription medicines approved for other conditions. Using any of them for dementia prevention or longevity is off-label and unproven. Semax, Selank, cerebrolysin, dihexa, P21, and BPC-157 are not FDA-approved for any use; this book reports their evidence, legal status, and risks only, and never how to obtain or use them.

Doses that appear in these pages are reported only as facts: what a trial tested, or what a forum member said he or she took. They are not recommendations, and this book contains no dosing, sourcing, or self-monitoring protocol. Do not start, stop, or change any medicine or supplement on the basis of this book. Decisions about prescription drugs, supplements, and testing belong in an accountable relationship with a licensed clinician who knows your history, diagnoses, and full medication list. Abruptly starting or stopping a prescription drug can itself cause harm. As of October 2026, the FDA-cleared Alzheimer's blood tests are for adults who already have symptoms; none is cleared to screen people without them.

Forum members are identified by the public usernames under which they posted, and their accounts are reported as testimony. Mention of a company, product, clinic, pharmacy, trial, or community is not an endorsement. The author and publisher disclaim liability for any loss or harm arising from the use or misuse of information in this book.

Evidence is labeled throughout by what it actually is:

- Forum account: a person's public report; evidence only of what that person said.
- Preclinical study: cells, tissues, or animals; useful for mechanisms, not proof of human benefit.
- Observational human study: an association measured without random assignment; vulnerable to confounding and selection.
- Conference abstract or preprint: a scientific report available before a complete peer-reviewed article; details and conclusions can change.
- Randomized controlled trial: the strongest ordinary design for causal treatment questions, while still limited by population, duration, size, adherence, endpoints, and execution.

Each claim also carries a grade on the series scale. A is a replicated clinical outcome in the relevant population. B is a controlled human signal with limits. B-null is controlled evidence of no effect on the endpoint tested. C is observational or uncontrolled human data. D is preclinical only. E is a forum account or hypothesis. Insufficient means nothing fits. Grades attach to a stated claim, not to a molecule: the same drug can earn an A for slowing decline after symptoms begin and Insufficient for preventing disease before them.

Trial statuses and publication stages in this edition were checked through October 10, 2026. They will change. That is why every chapter most exposed to coming results ends with a dated status box, and why the final chapter builds a watch list instead of a protocol.

If you think you may be having a serious reaction, infection, or other medical emergency, contact a clinician or emergency services immediately rather than relying on this text.

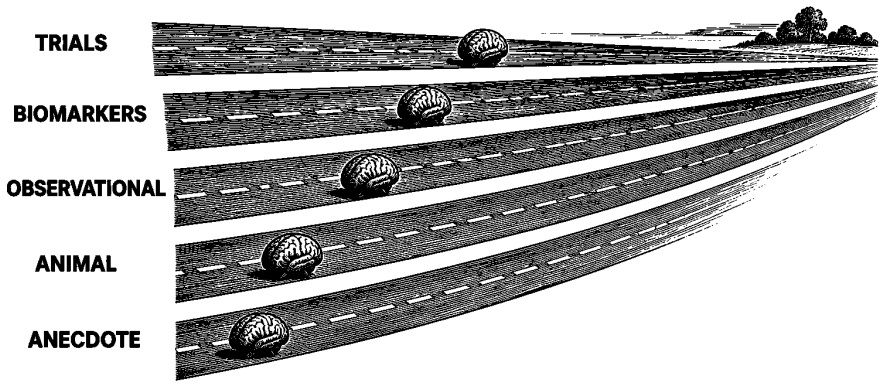


Figure 1. The evidence lanes. One claim can sit in several lanes at once, and this book grades each lane separately. "Trials" means randomized controlled trials with human clinical outcomes; a forum account is evidence only of what one person reported.

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Author's Note to the Expanded Edition

I did not spend eighteen months as a member of rapamycin.news. I went looking for a place where people were arguing, in public and in real time, about a disease that terrifies them. I read the archived sections used here the way a reporter reads a public record, not the way a member reads a home. That distinction matters enough to explain properly, because it shapes both what this account can claim and whose name belongs on its cover.

The July edition was built from a directed local crawl: 123 topics indexed, 114 fully fetched, and 7,872 posts preserved at the end of the July 2026 crawl. That was a substantial reporting corpus, not a complete mirror of the forum. Every direct quotation traced to a specific dated post in that frozen archive, rather than to a summary or my memory of reading it. When a member cited a study, I checked the paper, publisher record, or trial registry before using the claim as external evidence. Where I could not verify something, I tried to leave the uncertainty visible.

For this expanded edition, I returned to the public topic pages in October 2026 and refreshed the archive while respecting the site's robots instructions. The refresh added public material and let me check whether passages still appeared in their original context. It did not turn the project into an account of everything posted on the site. I used handles as published. I did not interview members or researchers, read private messages, or gain access to private areas. A later public reply can change the meaning of an earlier exchange; it cannot tell me what a participant meant privately. The dated post remains the unit of evidence for what a member said.

What changed between July and October was not merely the number of pages I had read. The prevention evidence moved. The first large randomized prevention evidence from blood-pressure control gave this book a stronger reason to distinguish a measured brain outcome from a plausible biological story. Other awaited results made that distinction harder to evade. The semaglutide EVOKE trials, VALAD, LATTICE, and NOPARK returned clean disappointments for hopes attached to them. STAREE delivered a split verdict rather than the simple answer readers on

either side of its debate might have preferred. As of October 2026, those results belong in the account, even where they interrupt a good story.

A failed trial does not prove that every related idea is worthless. It does mean that an attractive mechanism, an encouraging observational association, or a smaller earlier study cannot be spoken of as though the hoped-for clinical benefit had arrived. Equally, a positive result belongs to the people studied, the intervention tested, and the outcomes actually measured. It should not be stretched across every age, risk group, or version of an intervention. Much of the argument in this edition takes place in that narrow space between a result worth taking seriously and a conclusion the result cannot bear.

The subtitle changed for the same reason. The July edition's *before medicine catches up* captured a feeling I found in the forum: people did not believe they could wait, and they were searching among incomplete answers while conventional research proceeded at its own pace. I still recognize that feeling. But the phrase could suggest that medicine was standing still while the community worked, or that every experiment discussed here was simply early to a future vindication. Neither is a fair description of the record now. *What the evidence now says* puts the burden where it belongs. Some ideas have acquired better support. Some have met a decisive test and fallen short. Many remain open questions. The word *now* matters because this is a dated account of evidence, not a promise about what the next trial will find.

The book follows that evidence through five parts. Part I begins with the thread and the people in it, then sets out what the trials now say and what risk information can—and cannot—tell a person who has no symptoms. Part II takes up brain fuel, metabolic explanations, GLP-1 drugs, and vascular health. Part III considers exercise, sleep, sensory health, cognitive training, and hormones. Part IV enters the more speculative territory: cellular-energy claims, peptides, a physician's protocol, rapamycin, older drugs, devices, and supplements. Part V turns to the arrival of antibodies, the forum's mistakes, the limits of inference, and the difference between evidence ready to inform present decisions and questions still worth watching.

Those parts are arranged by subject, but the book also uses evidence lanes so that unlike claims are not made to compete on misleadingly equal terms. A population association is one kind of evidence; a mechanism observed in a laboratory is another; a randomized trial with a brain outcome is another

again. An intervention may improve a measure that matters to health without yet showing that it prevents dementia. A person's reported experience may be entirely sincere and still be unable to answer what would have happened without the intervention. The lanes keep those distinctions in view as the same idea travels from a forum post to a paper and, sometimes, into a trial.

The A–E grades are a compact way to show the state of support discussed in the text. They are not grades for a person's judgment, a ranking of moral worth among health concerns, or instructions to start or stop anything. They cannot erase differences between study populations or settle a disagreement about which outcome matters most. Their purpose is more modest: a reader should be able to tell whether a claim rests on replicated clinical outcomes, narrower or indirect evidence, or a proposal that remains largely untested. Four reference guides at the back gather the supporting distinctions in a form that can be consulted without asking the narrative chapters to behave like a manual.

This is Book Three of *The Longevity Evidence Series*. Books One, Two, and Four sit beside it, not beneath it. Each owns a different question; this book owns brain outcomes. That division matters because the same intervention can look promising against one measure and unconvincing against another. An argument about general longevity does not establish dementia prevention. Nor can evidence about a biomarker silently substitute for evidence about memory, function, or a diagnosis. I have tried to make this volume stand alone while keeping those boundaries intact.

Risk information requires an additional kind of restraint. A genetic result is not a forecast of an individual life. A blood marker under study is not, by virtue of being measurable, cleared to screen people without symptoms. Numbers can offer information while creating uncertainty about what to do with it. Genetic privacy has limits, too: GINA does not cover life, disability, or long-term-care insurance. Chapter 3 treats these as ethical questions as well as scientific ones, because the consequence of learning a number depends partly on what that number can establish and partly on what happens after it is known.

I am not a member of the community described here. I did not post in these threads, argue a dosing question, or share my own bloodwork. Nor did I interview the participants. My access is the public record and the external literature. One author's name carries the book while the people inside it remain sources, credited by the public handles under which they spoke.

Where the book could confirm a real name publicly attached to a handle, it uses that name.

I want to say plainly why I did not try to make this a co-authored project with the forum itself. The people quoted here are pseudonymous, and most did not write a single word expecting it to end up in a book. They cannot meaningfully consent to co-authorship, and they should not be expected to share whatever liability comes with a claim made casually in a discussion thread, at whatever hour they happened to be awake and worried. Treating them as sources, credited by the handle under which they actually spoke, is, I think, the honest form of respect.

A public thread is not a controlled interview. People misremember, round numbers, and cite studies from memory that turn out, on inspection, to say something slightly different. I have tried to catch those places and name them rather than quietly repair the record. The community's errors are not the point of this book. Neither are they evidence that concern makes people foolish. Some of the most impressive material I found consists of members correcting one another, reconsidering a claim, or admitting that a study they wanted to believe did not show what they had thought. The expanded edition owes them the same willingness to revise.

AI tools assisted the research and the drafting of this book, as they do elsewhere in this series. They helped search the archive, identify candidate papers, compare claims, work on prose, and develop figures and cover art. Their output was working material, not authority. I checked every source used to support the finished account; source classification, inclusion, interpretation, and revision remained my responsibility. The final evidence audit found errors that earlier tool-assisted passes had missed, including a conference abstract described too confidently as a peer-reviewed review. Correcting that error is part of the method, not an embarrassment to conceal. Errors that remain are mine.

This account offers education, not diagnosis or treatment advice, and it does not tell anyone what to take. Approved drugs are discussed within the limits of their labels; an off-label use is a question for a clinician, not a prescription from this book. Published evidence does not support prescribing a drug for dementia prevention on the strength of forum interest. Products outside established approval pathways receive scrutiny of their status, evidence, and risks, not instructions for using them.

Nothing in this book exists without specific people deciding, at specific hours, to type a fear or a citation or a piece of half-digested research into a

text box where a stranger might later find it. I am that stranger. I have tried to get it right. Wherever I have failed, the failure is mine, not theirs. I have tried to write about them the way I would want a stranger to write about me, if I were the one asking a website full of people I had never met whether it was too late to start.

Mark A. Smith
October 2026

Part I: The Question

Chapter 1: The Thread



Deborah Hall posted at 4:38 in the afternoon, Eastern time, on Easter Sunday.

Nothing in the post says where she was sitting, what the weather had done that day, or whether anyone else was in the house. Those details do not exist in the record, and these pages will not invent them. What exists is a time stamp. March 31, 2024, 20:38:39 UTC, and four paragraphs of careful prose typed into a text box on rapamycin.news, under the username Deborah_Hall.

Alzheimers is #1 in my priority of worries, she began. *At present, age 74, I have no issues or warning signs. But my mother, aunt and grandmother, all very long lived, have/had it.*

She described herself as well and fit, with no warning signs of cognitive trouble. Her A1C, a measure of average blood sugar, had held steady for years at 5.7 to 5.8. She was taking metformin and had ordered rapamycin. Neither drug had been established as a way to prevent Alzheimer's disease in someone like her; the product she had ordered was not an answer to the question she was about to ask.

Deborah had a theory about timing. She believed rapamycin might protect the brain before amyloid plaques formed but might become harmful after Alzheimer's-related changes were underway, when the cell's protein-clearing machinery could no longer respond as hoped. She also knew of a commercial blood test advertised as detecting Alzheimer's biomarkers before symptoms. It was not available in New York, where she lived. Could a test tell her which side of her proposed dividing line she occupied? At seventy-four, with her family history, was she too late to act?

Would welcome input on this, she wrote, posted a link to a Quest Diagnostics press release, and waited.

An Easter Sunday Question

She did not wait long. Thirty-one minutes later, Mouse_wont_die replied with an account of his mother, whose younger sister had died with Alzheimer's disease and who had begun showing noticeable short-term memory loss. He reported improvement after the family tried rapamycin, then stated the limit of his own story: *I can't say we have a cure. N=1, dramatic improvement though.*

That last phrase comes close to compressing the ethic of this website into a few words. *N=1* borrows the language of research for an observation involving one person. It can be an honest warning that the speaker cannot separate an intervention's effect from expectation, chance, other changes, or the uneven course of a condition. It can also sit beside a claim that feels, to the family living through it, too vivid to dismiss. The account is worth hearing as an account of what they saw. It cannot establish that rapamycin improved his mother's memory, much less that it would protect Deborah.

Seventeen minutes after Mouse_wont_die's reply, Dr.Bart brought a published scientist into the exchange. Responding to a request for references, he quoted Matt Kaeberlein on the possibility that rapamycin's effects might depend on disease stage. The passage included an important counterweight to Deborah's sharper version of the idea: *at least a subset of preclinical studies reported positive effects of rapamycin in mouse models even after substantial AD-like cognitive deficits and histopathology were present.*

The distinction was already visible before the thread was an hour old. Deborah had proposed a dividing line: before plaques, potential benefit; afterward, potential harm. The published discussion Dr.Bart cited entertained the question without establishing that line. It also described mouse studies, not a test that could classify a particular person or a trial showing that treatment at one stage helped while treatment at another caused decline. In the forum, a reader could see a hypothesis being challenged without seeing the fear beneath it resolved.

A little farther down that first evening, RapAdmin replied directly to Deborah with links to earlier forum conversations about rapamycin and Alzheimer's. Some concerned autophagy, the cellular process invoked in

claims about clearing unwanted material; others considered whether the drug's effects might differ across stages of disease. Deborah had not begun the discussion on this website. Her post became a place where existing arguments, new papers, and personal histories accumulated. The archive cannot tell us why that particular question drew so many people back, though asking for herself rather than merely circulating a study gave the exchange a human center.

The next morning, DrFraser introduced the "Type 3 Diabetes" theory, a proposed link between impaired brain insulin signaling and Alzheimer's disease. It would become one of the book's recurring questions. In the order of this conversation, though, it was not the beginning: family testimony and a scientist's qualified, stage-dependent hypothesis had reached Deborah first.

As the week went on, citation exchange began to resemble a support group. CuriousM described how demanding it felt to sustain changes involving food, exercise, meditation, and sleep. *None of them alone are that hard,* CuriousM wrote. *It's just doing all of it that becomes taxing.* Another member, medaura, offered a much more elaborate set of proposals for people carrying APOE ε4, the gene variant associated with increased Alzheimer's risk. The proposals mixed ordinary health practices with interventions for which dementia-prevention evidence was far weaker. A list can make unlike claims look equally settled when they are placed side by side.

Then medaura returned with a family story that resisted the tidy list. Two grandmothers carried the same APOE ε3/4 genotype but lived strikingly different cognitive histories. One had seemed mildly impaired for as long as medaura could remember. The other had poor health by several familiar measures and still lived to ninety-nine with only a relatively short period of mild impairment. Medaura offered no credential or theory that could account for the contrast. The story does not disprove a risk factor. It shows why a risk factor cannot write an individual biography in advance.

There is a trap on the other side, too. An exceptional relative who remains sharp into old age cannot show that inherited risk is meaningless, any more than a family marked by dementia can show that every descendant will become ill. Each account supplies a lived outcome without the comparison group needed to estimate what was likely beforehand. That is one reason a conversation can feel rich in evidence while leaving its central probability unanswered.

Desertshores contributed another kind of testimony. At an annual physical, he had passed brief cognitive tests while remaining troubled by everyday changes he noticed in himself. *I do not consider them helpful because I passed all of them easily. But, IMO that's because I was concentrating. My most common complaint now is 'Where did I put that.'* He recalled work as an electronics design engineer and described leaning more often on spell-check, along with changes in handwriting and punctuation. His post did not prove that a disease had begun. Neither did passing a test erase the difference he felt between his current habits and his earlier ones.

The archive records a group whose members were asking related but different questions. Deborah said she had no warning signs; desertshores described changes that bothered him despite passing tests; Mouse_wont_die described a family member with noticeable memory loss. A blood test proposed for assessment of someone with cognitive symptoms does not automatically answer a healthy person's question about future risk. Even the word *early* shifts meaning across these conversations: early symptoms, early pathology, and years before any symptoms are not interchangeable.

For principles of interpreting a single-person experiment without mistaking it for a clinical trial, see Book One, *The Longevity Operating System*, Chapter 11. The principle matters here less as a method than as a restraint. A forum can preserve details that a trial report cannot: the worry before a decision, the disappointment of an ambiguous result, the changes a family notices at breakfast. It cannot supply a control group after the fact. Memory itself is the outcome under discussion, making a retrospective account of improved memory especially difficult to test.

What Strangers Can, and Cannot. Know

By the second week, the thread had turned partly toward genetics. Neo discussed APOE and the steep rise in dementia risk with age, sometimes in language that made an individual future sound more certain than a population pattern permits. DrFraser shared his own result: *I have an E3/E4 so looks dismal by this graph without intervention.* The graph mattered to him because the number was his. But a chart built from groups does not reveal whether one person will develop dementia, at what age, or whether a proposed intervention will change the outcome.

A month into the thread, DrFraser said he was starting a blog series on preventing neurocognitive decline and wanted the forum's help sorting a

crowded field. *I appreciate all the citizen scientists on this board,* he wrote. *There is too much out there to filter through.* His presence gave the exchange a clinician who was willing to reason publicly, while leaving an ordinary reader with the same task as before: deciding which statements were supported by controlled evidence and which were a physician's extrapolations. The fact that a clinician participates in a discussion does not turn its other posts into clinical evidence.

The conversation kept widening. Members brought in studies of diet, twins, cognitive measures, and exceptional people who had not followed the course their genes seemed to predict. They challenged study methods and one another's reading of results. Occasionally they joked. These details matter because the thread was not a fixed doctrine being handed down to Deborah. It was a long, unfinished argument among people with different tolerances for uncertainty.

That uncertainty surfaced in an earlier forum discussion about Alzheimer's blood-test news. On January 27, 2024, adssx wrote, *I don't trust papers from big pharma. Especially on AD. The way they measure cognitive function is debatable. We want to see long-term data on use and whether it extends lifespan.*[1] The post concerned a broader dispute about evidence, not a validation study for Deborah's proposed test. Its useful question is what an outcome measure can establish. Distrusting a sponsor does not, by itself, invalidate a result; accepting a reported result does not extend it to outcomes or populations the study never measured.

The argument could also produce a dangerous impression of momentum. A new paper might answer a narrow laboratory question, yet appear in a stream of posts beside a personal account of someone trying an intervention. The next reader sees both as "what people are doing." In January 2025, DrFraser explained why he sometimes extrapolated from mechanisms when a study did not address an exact clinical question. That was an account of his reasoning, not independent evidence that any particular extrapolation worked.

As of October 2026, sirolimus, a form of rapamycin, is approved in the United States for specified medical uses including prevention of kidney-transplant rejection; it is not approved for aging, longevity, or dementia prevention. Its prescribing information carries a boxed warning concerning immunosuppression, infection, and malignancy. Those facts do not decide every research question about rapamycin and the brain. They do set a boundary around what a reply to Deborah could honestly have

established in 2024: neither an encouraging family account nor a plausible cellular mechanism could tell her that using it would prevent Alzheimer's disease. The evidence in this book does not support prescribing it for that purpose.

There is a second boundary, concerning the question of testing. In 2020, the U.S. Preventive Services Task Force concluded that evidence was insufficient to assess the balance of benefits and harms of screening community-dwelling adults aged sixty-five or older for cognitive impairment when they had no recognized signs or symptoms. That statement was about screening; it did not address the evaluation of a person who reports symptoms.[2] Deborah's post described fear and family history, but no warning signs. It should not be silently recast as the same clinical situation as desertshores's complaint, or as the symptomatic patients enrolled in diagnostic-test studies.

An insufficient-evidence finding is not a finding that screening can never help. Nor is it an invitation to assume that an available test must help until someone proves otherwise. Screening asks whether testing people who have not come forward with a problem improves outcomes enough to justify false alarms, inconclusive findings, and subsequent evaluation. Diagnostic accuracy is one part of that question. Whether knowing a result changes what happens to people is another.

In the earlier forum thread, Neo asked on January 28, 2024, of a reported test: *Is it a full FDA approval? Have people seen any papers?*[3] Those are better questions than assuming that "available" means "validated for me." They are not, on their own, enough. Regulatory status has to be paired with the test's stated purpose and the population in which its accuracy was measured.

The original Easter exchange belongs in this book as an archive of questions, not as a source of clinical recommendations. Its timestamps show what members knew, suspected, and contested at a particular moment. Later studies can check claims the members made; they cannot retroactively make an anecdote into a trial. Nor does finding that a hypothesis resembles later researchers' language show that the member who raised it had discovered a reliable rule. Deborah's question deserves more than either easy dismissal or retrospective credit for being right.

The Test Moves Into Clinics

The clinical facts changed after Deborah posted. As of October 2026, the first FDA-cleared blood test used to aid Alzheimer's assessment was Fujirebio's Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio, cleared in May 2025 for adults fifty-five and older who have signs and symptoms of cognitive decline. It is not intended to screen people without symptoms or to make a stand-alone diagnosis; its results must be considered alongside other clinical information.[4] The change was substantial for the indicated patient. It was not a clearance of the test Deborah had asked about, nor an endorsement of blood testing as a way for a healthy person to find out whether she was "too late."

The FDA-reviewed study for Lumipulse compared 499 plasma samples from cognitively impaired adults with amyloid PET or cerebrospinal-fluid findings. Among positive blood-test results, 91.7 percent corresponded to evidence of amyloid plaques by those comparison methods; among negative results, 97.3 percent corresponded to a negative PET or CSF result. Fewer than 20 percent of results were indeterminate.[4] The figures tell us how a test performed in the population and comparison used for its review. They do not say that a positive result in an asymptomatic seventy-four-year-old predicts her chance of dementia, or that a negative one settles her future.

Those two percentages can sound like promises about an individual result. They are proportions calculated among results in the reviewed sample, not universal properties that stay fixed when the test is used elsewhere. If the share of people with the measured pathology differs between a symptomatic evaluation group and a group without symptoms, the fraction of positive results that correspond to pathology may differ as well. More accurate detection of pathology would still leave open a separate question: which people with that pathology will develop cognitive impairment.

There is a human reason that qualification can be hard to hear. Someone who has watched three older relatives develop dementia is not asking an abstract question about the agreement between laboratory methods. She may be asking whether an ordinary afternoon, apparently free of symptoms, conceals a process already beyond repair. Amyloid pathology, a measurable blood signal, a diagnosis, and a future loss of independence are linked questions, but they are not the same event. Test accuracy for one cannot be presented as certainty about all the others.

The route into clinical assessment widened as another test received clearance. As of October 2026, Roche's Elecsys Phospho-Tau (217P) Plasma had FDA clearance to aid assessment of amyloid pathology in adults fifty-five and older with signs, symptoms, or complaints of cognitive decline, across primary and specialty care. Like Lumipulse, it was not cleared to screen people without symptoms.[4,5] The two tests also report different measurements: one uses a p-tau217-to-amyloid ratio, while Elecsys pTau217 measures a single biomarker.[4,5] "A blood test for Alzheimer's" is therefore not the name of one uniform tool.

Roche announced the Elecsys pTau217 clearance on August 24, 2026. The test reports positive, intermediate, or negative categories to support clinical assessment. Roche says it is not a stand-alone test and has not been established for predicting who will develop dementia or for monitoring treatment effects.[5] That last sentence bears directly on Deborah's original hope. A test may become easier for a clinician to use while remaining unable to answer a healthy person's question about whether a drug should be started.

The validation data are impressive within their proper frame. In a retrospective analysis of stored samples from two prospective biomarker-validation studies, researchers examined 303 memory-clinic patients with mild cognitive impairment or mild dementia. Against a cerebrospinal-fluid reference measure, Elecsys plasma p-tau217 achieved an area under the curve, or AUC, of 0.93, compared with 0.87 for p-tau181. Using two thresholds, the researchers obtained 95 percent specificity at the upper cutoff and 95 percent sensitivity at the lower cutoff; 27 percent of cases fell between them, in an indeterminate range.[6]

An AUC describes how well a test separates comparison groups across possible thresholds. It is not the probability that a given patient has Alzheimer's disease, and still less the probability that an apparently healthy person will develop symptoms years later. The indeterminate group also has a clinical reality behind its percentage: more than a quarter of this symptomatic cohort did not fall cleanly into either end of that two-threshold strategy.[6] An intermediate result may leave a clinician considering what other information is needed. By itself, it cannot give the person reading it the certainty she came looking for.

The two-threshold design reflects a tradeoff rather than a defect that better advertising could erase. Setting a demanding bar for a positive result can reduce false positives at that end; setting a separate bar for a negative result

can reduce missed cases at the other. The space between protects against forcing borderline measurements into confident categories. It also means that "I took the test" will not always be followed by "I got a clear answer." In the reported 303-patient analysis, that middle category contained 27 percent of cases.[6]

The memory-clinic cohort had cognitive symptoms. It did not establish how accurately the test would classify people without symptoms, or what benefit would follow from testing them.[6] This is not a technicality inserted to spoil a promising result. When a test moves from a clinic serving people already under evaluation into a population whose members mostly will not develop symptoms soon, the meaning of a positive result can change. Follow-up may uncover a useful explanation for a patient's complaint; it may also generate prolonged uncertainty when there was no complaint to explain.

One can respect the diagnostic progress without assigning it a prevention grade it has not earned. On this book's evidence scale, p-tau217 blood tests are n/a, diagnostic: their accuracy has been studied in symptomatic patients, and cleared uses concern assessment of symptomatic adults, not screening. No published study has shown that blood biomarker testing prevents dementia or slows cognitive decline.[4,5,6] A diagnostic category is not a low mark for a potentially useful diagnostic test. It means the prevention question and the assessment question must be graded separately.

For how to prepare questions about a proposed test for an appointment, see Book One, *The Longevity Operating System*, Clinician Conversation Handbook. The cross-reference is about the setting in which a result can be interpreted, not a suggestion that everyone needs testing. A clinical evaluation can consider what change prompted concern, what else might explain it, and what a positive, negative, or intermediate result could mean. A number delivered without that setting cannot do those things.

A Result Is Not a Forecast

Testing did not remain confined to clinics. AARP reported in December 2025 that direct-to-consumer services were offering Alzheimer's blood biomarker packages, including p-tau217, without requiring a doctor's order. Experts quoted in its account cautioned that a blood biomarker is one tool rather than a stand-alone diagnosis, and that consumers may receive results without the cognitive evaluation needed to interpret them.[7] By September 2026, the Associated Press was describing both FDA-cleared tests intended to help evaluate symptoms and separate tests offered through laboratories and online services; the dementia specialists it consulted did not recommend such testing for people without symptoms outside research studies.[8]

The appeal of a result obtained outside a clinical evaluation is easy to understand in the light of Deborah's post. A person with family history may not want to wait until a change is obvious to others. Testing can look like a way to make uncertainty smaller before approaching a clinic. Yet a result can create a new uncertainty: whether the finding is relevant to the person's present cognition, whether it warrants further evaluation, and what to make of it if no established prevention decision follows. Those questions become harder, not easier, when a test is presented without a defined clinical use.

The word *prediction* needs particular care. Research can identify a relationship between a biomarker measured today and impairment observed later in a group. That relationship may be scientifically valuable while remaining a poor basis for telling one individual what will happen. A September 2026 news account summarized a cohort estimate that older adults with very high p-tau217 had a 38 percent risk of cognitive impairment within five years. It also stressed that a positive biomarker is a risk indicator, not a guarantee of future Alzheimer's symptoms.[8] Put another way, that reported estimate was not a forecast that all, or even most, people in the high-biomarker group would become impaired during that period. It does not say that changing the biomarker would change the outcome, either.

The forum's later blood-test conversations show the attraction of finding an earlier warning. In May 2026, RapAdmin circulated an account of research suggesting that a blood test in middle age might indicate who was more likely to show diminished cognition despite having no dementia symptoms.[9] Such a study can generate a research question about

prediction. It does not expand the cleared indication of a diagnostic test to screening or establish that acting on an early result prevents dementia. The distance between "associated with a later outcome" and "useful for deciding what this healthy person should do now" is where much prevention hype gathers.

Another forum discussion, on September 10, 2026, turned to GDF15, a different blood protein. RapAdmin described a reported association between higher levels and later brain disorders, then posed a more difficult question: *Are there any well-validated approaches to lowering (or keeping low) GDF15 levels in humans or mammals?*[10] The question exposes a common reversal in biomarker thinking. A substance associated with illness might reflect an underlying process rather than cause it. Even if a measurement helps sort future risk in a research cohort, lowering the measurement has not thereby been shown to lower the risk.

Deborah's own stage-dependent theory occupied that distance. A later conference abstract compared small human rapamycin research programs involving people at different points along the cognitive spectrum and raised the possibility that disease stage affected biomarker responses. The programs differed in their participants and designs. Their reported changes in imaging or injury-related markers were not demonstrations of delayed dementia in healthy people or accelerated decline in symptomatic people. The similarities between the researchers' question and Deborah's do not establish the rule she needed: before plaques, help; after plaques, harm.

The possibility of being wrong in either direction is more than an academic concern. If a reader treats an unclear blood result as proof that prevention is already futile, the test may do harm without clarifying disease. If a reader treats a reassuring result as permission to ignore an emerging cognitive complaint, a different opportunity for assessment may be missed. And if a reader takes either result as an instruction to use a drug outside its approved purpose, diagnostic information has been made to carry a treatment claim it was never shown to support. These are possible failures of interpretation, not predictions about what would have happened to Deborah.

What the Easter thread could give her was companionship in uncertainty. Mouse_wont_die gave a family observation and labeled its limit. Dr.Bart pointed to a published qualification of the hypothesis she had brought. Other members offered papers, theories, burdensome routines, contrasting family histories, and accounts of changes they could feel but could not fully

explain. The thread could not examine Deborah, determine whether she had amyloid pathology, establish whether rapamycin would help or hurt her, or convert family history into a personal forecast.

Nor can the newer tests close that gap merely by existing. As of October 2026, the FDA-cleared Alzheimer's blood tests described here aid assessment in specified populations with cognitive signs, symptoms, or complaints; neither is cleared to screen people without symptoms.[4,5] Their arrival makes it more necessary to ask what question a result answers. For some symptomatic patients, evidence about underlying pathology can contribute to an evaluation. For Deborah as she described herself that Sunday, seventy-four, worried, and without warning signs, the test she imagined was being asked to do something else: settle a prevention decision whose premise had not been clinically established.[4,5]

The original post ended with a request for input, not a verdict. Two and a half years of argument and a changing diagnostic field have made parts of the question more precise. They have not produced an online reply, a blood value, or an individualized prevention prescription that the evidence can justify. The trials in the next chapter ask what interventions have actually changed cognitive outcomes, in whom, and over what period. That is a different way to honor Deborah's question from pretending the thread could have answered it.

Chapter 2: What the Trials Now Say



On August 1, 2026, RapAdmin posted a summary of a podcast conversation with neurologists Dean and Aisha Sherzai under the title “The Critical Decades: How Daily Habits in Midlife Can Actively Delay Cognitive Decline.” The summary presented Alzheimer’s disease and vascular dementias as processes that can begin well before symptoms appear.[1] That long lead time makes an argument for attending to ordinary habits. It also sharpens the question: which changes have actually been tested against a comparison group, and what happened?

A blood-pressure trial counted dementia diagnoses. Three lifestyle trials measured performance on cognitive tests. A training trial later linked participants to insurance records. These are not interchangeable answers. A person can do better on a test without having been shown less likely to develop dementia; a program can be sensible for general health without having passed either test. This chapter sets the yardstick before the more personal chapters take up risk, interventions, and the appeal of doing something now.

For the general hierarchy of evidence used throughout this series, see Book One, *The Longevity Operating System*, Chapter 2, “The Hierarchy of Evidence.”

The Estimate Is Not a Promise

The 2024 *Lancet* Commission identified fourteen potentially modifiable dementia risk factors: less education, hearing loss, high LDL cholesterol, depression, traumatic brain injury, physical inactivity, smoking, diabetes, high blood pressure, obesity, excessive alcohol use, social isolation, air pollution, and untreated vision loss. High LDL cholesterol and untreated vision loss were additions to its earlier accounting. The commission estimated that these factors together accounted for about 45 percent of dementia cases worldwide at the population level under its modeling assumptions.[2]

That 45 percent is often made to carry more weight than it can bear. A population-attributable estimate asks, in effect, how much disease might be associated with a set of exposures across a population if the assumed relationships are causal and the exposures could be changed. It is not a trial result showing that a package of interventions prevented 45 percent of cases. It is not the portion of any one reader's risk that remains available to erase. Nor can the percentages attached to individual factors simply be added without accounting for overlap: the person with hypertension may also have diabetes, hearing loss, or little opportunity for exercise.

The list matters nevertheless. It moves attention beyond an imagined single cause and toward conditions that accumulate across a lifetime. It also mixes quite different kinds of factors. A diagnosis of hypertension is not the same sort of exposure as air pollution; years of schooling cannot be added to a seventy-year-old's past in the way a hearing aid can address hearing loss now. Some factors are amenable to randomized intervention studies. Others are difficult to change, difficult to assign randomly, or entangled with income and access to care. A commission's risk-factor map is therefore a research agenda, not a fourteen-part prescription.

The distinction becomes particularly sharp when an association has an established cardiovascular treatment. High LDL cholesterol belongs on the commission's dementia-risk list, but that does not itself show that prescribing an LDL-lowering drug prevents dementia. In STAREE, 9,971 community-dwelling adults aged seventy or older without cardiovascular disease, diabetes, or dementia were randomized to atorvastatin or placebo. Over a median 5.9 years, the composite outcome of death, dementia, or persistent physical disability did not differ significantly, although major cardiovascular events were lower in the atorvastatin group. The reported composite cannot establish a standalone dementia-prevention benefit.[3] A

treatment can have an important reason for use without acquiring every hoped-for benefit suggested by its risk factor.

The reverse mistake is possible, too: demanding a completed dementia-prevention trial before taking any ordinary health problem seriously. The National Institute on Aging's July 2026 review says that nothing has yet been proved to prevent Alzheimer's disease, while describing blood-pressure management, physical activity, and other general health measures as reasonable steps.[4] That is a carefully bounded position. General health benefits and a plausible effect on future cognitive risk are not the same as proof of preventing Alzheimer's disease.

A further complication is that *dementia* and *Alzheimer's disease* do not name identical outcomes. Dementia is a clinical syndrome with multiple causes and mixed forms; Alzheimer's disease is one possible underlying pathology. A study counting all-cause dementia may capture effects on vascular injury even if it cannot isolate an effect on Alzheimer's pathology. A study reporting a better cognitive score may be detecting a change in attention or test performance rather than a change in either pathology. The outcome in a headline needs to match the outcome the investigators measured.



Figure 2. The 2024 Lancet Commission's 14 potentially modifiable risk factors. The often-quoted figure of about 45 percent is a population-attributable estimate built on modeling assumptions, not the measured result of a prevention trial (Livingston et al., Lancet, 2024).

For the series-wide account of dementia prevention and its limits, see Book One, *The Longevity Operating System*, Chapter 15, "Dementia Prevention Without Magical Thinking."

Three Multidomain Experiments

FINGER provided an influential controlled test of an appealing proposition: rather than change one behavior, support several at once. The Finnish trial randomized 1,260 at-risk adults aged sixty to seventy-seven to a two-year program combining diet, exercise, cognitive training, and vascular-risk monitoring, or to general health advice. At two years, the intervention group had a better result on the total score of a neuropsychological test battery; the between-group difference in annual change was 0.022, with a 95 percent confidence interval of 0.002 to 0.042.[5] The number is small, but it is a measured difference against a randomized comparator, not a participant's impression that thinking feels clearer.

FINGER did not establish that the program reduced dementia incidence. Its published result concerned cognitive performance over two years in an at-risk older population, not the proportion receiving a dementia diagnosis years later.[5] That limit does not cancel the finding. It locates it. Better scores might represent a valuable gain in function, an early sign of a longer-term effect, or a difference that does not grow into fewer diagnoses. The trial alone cannot decide among those possibilities.

The program's many components create another limit. Because diet, exercise, training, and vascular monitoring arrived together, the trial cannot tell us how much of the measured difference came from any single part. That is partly the point of a multidomain intervention: health problems rarely arrive one at a time. But the design cannot be used to certify a favorite ingredient. Someone who likes cognitive games cannot claim FINGER as a trial of games alone; someone who favors a particular diet cannot claim it as a trial of that diet alone.

US POINTER asked a somewhat different question. It randomized 2,111 at-risk adults aged sixty to seventy-nine to structured or self-guided multidomain lifestyle programs for two years. Both groups improved on the global-cognition measure, and the structured group improved more: a between-group difference of 0.029 standard deviations per year. The trial did not test dementia incidence.[6] Its comparator matters. This was not a comparison between intensive help and a group told to ignore its health; it

tested what additional structure could achieve beyond a self-guided approach.

That makes the finding more relevant to the unglamorous work of delivery. Information alone is not the same thing as organized support, repeated contact, and help sustaining a plan. Yet a small average advantage for structure does not tell us which participants benefited most or whether the same structure would work equally well when offered outside a trial. Nor does improvement within both groups prove that both programs caused improvement: people may become familiar with tests, and cognitive scores can change for reasons other than the assigned intervention. Randomization most securely supports the *difference between groups*.

LatAm-FINGERS extended the question to another setting. Across eleven Latin American countries, investigators randomized 1,065 adults aged sixty to seventy-seven at elevated dementia risk to a two-year systematic or flexible lifestyle intervention. Mean annual change in global cognition was 0.31 standard deviations in the systematic group and 0.20 in the flexible group, a between-group difference of 0.11 standard deviations per year. About 82 percent completed two-year follow-up; mean adherence in the systematic group was 71.6 percent. The study reported more adverse events in that group, though none of the serious adverse events was judged related to the intervention.[7]

The result strengthens the case that organized multidomain programs can affect measured cognition in more than one country and health system. It does not turn the three trials into a head-to-head contest. Their participants, comparators, measures, and delivery settings differed. LatAm-FINGERS' larger reported difference does not demonstrate that its particular program is inherently more effective than FINGER or US POINTER. The fair comparison is within each randomized trial, where assignment balanced the groups that its investigators actually studied.

Delivery is part of the intervention. In a trial, reminders, staff time, assessment visits, and a shared understanding that participants are being observed may help sustain participation. In routine life, transportation, paid work, caregiving, disability, and the availability of safe places to be active can decide whether an attractive program is usable. Those practical barriers are not arguments against the trials. They explain why an effect measured under organized conditions cannot be assumed to appear at the same size whenever a pamphlet lists the same activities.

There is also a question of whose cognition the tests capture. A composite score can detect changes across several abilities that would be hard to notice in daily conversation. That sensitivity is useful when dementia diagnoses are still uncommon during a short trial. But a composite is constructed from tests and their weighting; it is not a count of people who kept a job, managed household affairs, or avoided needing care. The trials give a controlled signal on the measures they chose. Longer follow-up with clinical outcomes would answer a different and more demanding question.

A June 2026 review of randomized non-drug interventions in lower- and middle-income countries found positive pooled cognitive effects for multidomain programs in selected studies, alongside significant publication bias. Its participants had mild cognitive impairment or subjective cognitive concerns, so its result does not directly establish dementia prevention in cognitively unimpaired adults.[8] The publication-bias warning deserves attention: if studies with disappointing results are less likely to appear, a pooled estimate can flatter an intervention even when the included trials were conducted carefully.

For multidomain lifestyle programs, the series grade is B for small cognitive gains, not a demonstrated dementia endpoint. Here B means a controlled human signal with limits. The grade belongs to the specific claim that organized programs can produce favorable measured cognitive outcomes in at-risk older adults, supported across FINGER, US POINTER, and LatAm-FINGERS. It does not promote that result into proven prevention of a dementia diagnosis.[5,6,7]

The breadth of these programs is both their appeal and their interpretive price. A person may reasonably value movement, food quality, social contact, and attention to vascular health for reasons other than dementia. But when the result is attributed to “lifestyle,” it becomes easy to smuggle an untested activity into the successful package or to assume that doing one part reproduces the trial. The experiments support the tested comparisons. They do not license every adjacent claim about brain health.

Pressure and Practice

A result closer to the outcome readers most want comes from the China Rural Hypertension Control Program, or CRHCP. Investigators randomized 326 villages in rural China, encompassing 33,995 adults aged forty or older with uncontrolled hypertension, to village-doctor-led intensive blood-pressure control or usual care. At forty-eight months, all-cause dementia was less frequent in the intervention group: risk ratio 0.85, with a 95 percent confidence interval of 0.76 to 0.95. Serious adverse events were also fewer in that group.[9] Unlike the multidomain trials just discussed, this study counted dementia rather than relying only on cognitive-test change.

A seven-year follow-up reported dementia in 8.85 percent of the intervention group and 10.55 percent of usual care, with an adjusted risk ratio of 0.85. Those figures were presented at a 2026 cardiology conference; they are longer follow-up from the same CRHCP trial, not a second independent randomized experiment.[10] The distinction matters because a repeated finding in one cohort helps assess durability, while replication in a different population would test how well it travels.

CRHCP is the strongest blood-pressure result in this book because it reports a favorable randomized dementia outcome in people with uncontrolled hypertension. It is not a warrant to transfer its program wholesale to every older adult or to specify a universal blood-pressure target here. The intervention was delivered through a particular village-doctor system to a particular enrolled population, and clinical choices must account for an individual's circumstances. Chapter 7 takes up targets, adverse effects, and interpretation in their proper setting.[9]

SPRINT MIND illustrates why the wording "blood pressure prevents dementia" still outruns the complete evidence. Among adults with hypertension, intensive control reduced mild cognitive impairment and the combined outcome of mild cognitive impairment or dementia. Its reduction in probable dementia alone was not statistically significant: hazard ratio 0.83, with a 95 percent confidence interval of 0.67 to 1.04. The trial stopped its intervention early because of cardiovascular benefit.[11] A nonsignificant dementia result is not proof of no effect, just as a significant related outcome is not proof of a dementia effect. The two studies are informative precisely because their populations, delivery, and measured results are not identical.

Cognitive training supplies a different kind of test. ACTIVE enrolled 2,802 older adults in 1998–99 and compared several kinds of training. In a Medicare-linked analysis extending up to twenty years, the speed-of-processing training group that also received boosters had lower recorded dementia incidence than controls: 105 of 264 participants, or 40 percent, versus 239 of 491 controls, or 49 percent; hazard ratio 0.75, with a 95 percent confidence interval of 0.59 to 0.95. Speed training without boosters, and the memory and reasoning training arms, did not show statistically significant effects in that analysis.[12]

This is a narrow, long-term signal, not a finding that "brain games prevent dementia." The qualifier about boosters is part of the result; so is the absence of significant findings for the other training arms. The Medicare-linked outcome also differs from a prospectively assigned clinical assessment of every participant twenty years later. Claims data can make unusually long follow-up possible, but the study's particular training task and later method of identifying dementia constrain what can be inferred about a new commercial game or a casual puzzle habit.

A plausible explanation should not be confused with a demonstrated mechanism. Speed training might improve a skill that transfers to everyday functioning. It might help people compensate for changes that still occur. Or the long-term association might depend on features of the original intervention and follow-up that a consumer product does not share. ACTIVE raises a worthwhile research question and reports a meaningful signal for one arm; it does not dissolve those alternatives. Its series grade is B for that narrow claim, a controlled human signal with limits, not a blanket grade for cognitive training.[12]

The tension between pressure and practice is useful. Blood-pressure care begins with a recognized health condition and, in CRHCP, reached a dementia endpoint. ACTIVE begins with training a mental operation and suggests a later difference in recorded diagnoses, but only for a specified arm. Both are more informative than a claim that keeping busy must protect the brain. Neither says that an intervention which feels mentally demanding will reproduce the outcome.

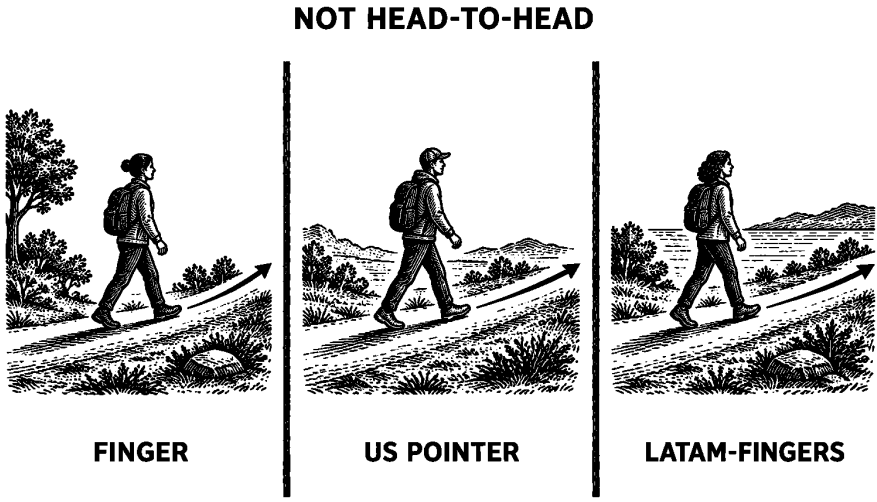


Figure 3. Three multidomain lifestyle trials: FINGER (Finland, 2 years), US POINTER (2,111 adults aged 60–79; the structured program beat the self-guided one by 0.029 standard deviations per year in global cognition) and LatAm-FINGERS (2 years). All measured cognitive test scores, not dementia incidence, and their populations and comparison arms differ, so they are not a head-to-head contest.

The Modest-Effects Baseline

Small cognitive differences are easy to mishandle in either direction. A change measured in hundredths of a standard deviation per year can sound too small to matter to anyone. A statistically significant result can sound like the first installment of a large protective effect. Neither reaction reads the trial closely. Statistical testing asks whether an observed between-group difference is reasonably distinguishable from chance under a model; it does not announce how many people will avoid a diagnosis, nor how conspicuous the average difference would be in a household.

Follow-up length is part of the answer. Dementia usually develops over years, and a two-year study can be well designed yet poorly positioned to count enough diagnoses to resolve a modest effect on incidence. Researchers may choose cognitive tests because they can register earlier differences in a feasible trial. That choice is defensible, provided the eventual account preserves the word *cognition*. Calling such a result "dementia prevention" skips the step the study was not built to test.

The population also sets the reach of a result. FINGER, US POINTER, and LatAm-FINGERS enrolled older adults at elevated risk rather than a random cross-section of all ages.[5,6,7] A program could have a detectable average effect there and a different effect among younger, lower-risk people. Conversely, a study limited to older adults cannot settle the forum's question about the full span of midlife. Early action may be appealing, but these multidomain trials did not follow people from midlife through the decades in which dementia diagnoses would be counted.

Participation makes interpretation less tidy still. LatAm-FINGERS retained about 82 percent of participants at two years, a substantial achievement for a multicountry behavioral study but not complete observation of everyone randomized.[7] Whenever some participants are missing at follow-up, investigators must consider whether their outcomes might have differed from those who remained. Adherence tells another story: a program that helps only when people can stay engaged may have a sound biological premise but limited practical reach. The resulting trial estimate describes the tested offer and its actual uptake, not an imaginary world of perfect participation.

Outside trials, observations can add context without replacing the controlled comparison. A cohort of 8,189 older U.S. Adults found moderate-to-high digital isolation associated with greater dementia risk than low digital isolation after adjustment for measured factors. It cannot establish that introducing digital engagement would prevent dementia.[13] Digital isolation may reflect limited access, sensory problems, poor health, or existing cognitive change. The observation may identify a vulnerable group while leaving the effect of a digital intervention unanswered.

The same restraint applies to socially and intellectually valued pursuits. A meta-analysis found that bilingual participants were, on average, older at observed dementia symptom onset, but its studies of dementia incidence did not provide strong evidence of prevention.[14] In two research cohorts, higher education was more consistently associated with baseline cognitive performance than with later cognitive change.[15] Such findings can fit ideas about cognitive reserve without proving that starting a language course late in life or adding years of education after the fact prevents disease.

Even when an intervention changes an experience it was designed to change, it may not be distinctive. In a Hong Kong trial of 245 lonely older adults, loneliness improved within both a mindfulness group and a social-contact comparison group, but mindfulness was not superior to

social contact at twelve months on the primary loneliness outcome. The study did not measure dementia prevention.[16] Its comparison is a useful reminder that the company, attention, and regular meetings surrounding an activity can matter. A trial needs a comparator capable of revealing what the featured ingredient adds.

Uncertainty about alcohol offers a related warning against turning an observational curve into an invitation. A 2026 synthesis of twenty cohorts found uncertain evidence that low-to-moderate alcohol intake protects cognitive function; higher intake was associated with lower cognitive function in analyses accounting for baseline cognition.[17] In a separate study of middle-aged and older participants, moderate-to-severe alcohol use disorder was associated with greater reported cognitive decline.[18] Neither result supports presenting alcohol as a brain-protection intervention.

This baseline, small controlled cognitive gains, selected longer-term signals, and more tentative observational associations, may feel unsatisfying beside a confident claim that a few habits can keep Alzheimer's away. It is more useful. It permits genuine positive findings to stand without requiring them to answer questions they never tested. It also leaves room for established reasons to address hearing, vision, social connection, cardiovascular health, or loneliness without relabeling every benefit as proven dementia prevention.

What Prevention Has Not Yet Shown

As of October 2026, the strongest supported statement for the three multidomain lifestyle trials is that structured programs produced favorable measured cognitive outcomes relative to their own comparators in at-risk older adults. None established reduced dementia incidence.[5,6,7] CRHCP supplies a randomized all-cause dementia outcome in adults with uncontrolled hypertension; its favorable seven-year report remains follow-up from the same trial.[9,10] ACTIVE supplies a narrower, claims-linked long-term dementia signal for speed training with boosters, not for every kind of training it tested.[12]

These differences are not editorial fine print. They determine whether the reader is hearing about a risk factor, a surrogate measure, a controlled cognitive result, or a clinical outcome. A favorable finding at one level can justify the next experiment, but it cannot silently substitute for that experiment. A proposal to combine interventions is still a proposal: the

lifestyle-plus-drug PROTECT-Cog trial was announced in 2026, and as of October 2026, no efficacy result for the combination had been published.[19]

There is a particular temptation to make the prevention claim by accumulation. If exercise, diet, cognitive activity, and vascular care each sound plausible, their combination may sound inevitable. Multidomain trials give that combination a better footing than plausibility alone, but they do not identify every active component or prove that more components always bring more benefit. Extra demands can reduce adherence, consume time and money, or compete with care that has a clearer indication. LatAm-FINGERS reported more adverse events in its systematic group, even though none of the serious events was judged intervention-related.[7] "Lifestyle" should not be treated as synonymous with effortless or consequence-free.

The distinction between avoiding disease and living better before disease is also worth keeping. A small improvement in a cognitive measure might be valuable even if it never produces a detectable change in dementia incidence. A person who becomes more physically capable or more connected to others may gain something real that a dementia trial was not designed to count. Equally, those other benefits must not be offered as proof of an Alzheimer's outcome. Accurate claims leave room for several kinds of value without merging them.

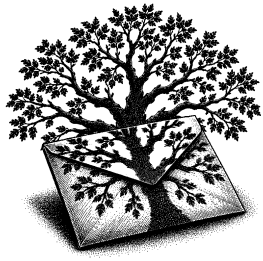
The World Health Organization's second-edition dementia-risk-reduction guidance, published in July 2026, drew on systematic evidence reviews. For vision-impairment interventions specifically, it found insufficient evidence to recommend them *for dementia-risk reduction*: the reviewed dementia evidence consisted of observational cataract-surgery studies in adults with normal cognition and was judged very low certainty.[20] That conclusion does not say vision problems are unimportant or that their correction has no purpose. It shows how carefully a guideline can separate a sound intervention for one reason from an unproved claim for another.

The National Institute on Aging draws the broader boundary plainly: nothing has yet been proven to prevent Alzheimer's disease, while research continues on blood pressure, physical activity, cognitive training, and other factors.[4] The wording is not a dismissal of every trial in this chapter. "Alzheimer's disease prevention" is a harder, more specific claim than a favorable cognitive score or even fewer cases of all-cause dementia in one hypertension trial. Evidence can advance without all claims advancing together.

Population trends do not supply the missing individual answer. The Alzheimer's Association's 2026 review estimated that 7.4 million Americans aged sixty-five or older were living with clinical Alzheimer's dementia that year, a count of people living with the condition, not the number of new cases. It reported mixed evidence that dementia incidence may have declined in some high-income countries through 2018 and said it was unclear whether those declines continued afterward. The number of people affected can rise as the older population grows even where incidence at a given age falls.[21] Neither trend tells a reader what a newly adopted program will do for that reader.

The forum's critical-decades question therefore remains open in its strongest form. The years before symptoms may offer opportunities to protect general health and perhaps influence later cognitive risk. The trials show that some organized changes can move cognitive measures and that intensive blood-pressure control, in a defined population, can reduce an all-cause dementia outcome. They do not offer an individual guarantee, a 45-percent reduction to claim, or a universal package known to prevent Alzheimer's disease. The next question is how a person comes to know, or thinks they know, what risk they carry.

Chapter 3: Knowing Your Risk: APOE4, p-tau217, and the Ethics of a Number



On May 31, 2026, RapAdmin opened a public thread titled “Can an Alzheimer’s Blood Test Detect Early, Subtle Cognitive Decline?” The post described research suggesting that a blood test in middle-aged adults might identify people more likely to show diminished cognition “even without any dementia symptoms.”[1] It was a small public question with a large private shadow. In the July material, a different concern ran alongside it: what an APOE4 result might mean to someone who had watched Alzheimer’s disease in the family. One question began with a marker in blood; the other, with an inherited variant. Both asked whether knowledge could arrive before a person knew what to do with it.

This chapter slows down after the trial survey in Chapter 2. A test can be accurate for one purpose and poorly suited to another. A genetic finding can describe a striking pattern across thousands of people without supplying a date for any one of them. And a result that seems private may affect conversations with relatives, clinicians, and insurers. Those are not objections to knowing. They are reasons to ask what, precisely, a number establishes, and what it leaves unresolved.

A Genotype Is Not a Date

APOE is a gene involved in lipid transport, and its ε4 variant is associated with Alzheimer's disease risk. The strongest genetic claim in this chapter concerns people who carry two copies of ε4, often called APOE4 homozygotes. In 2024, researchers examining 3,297 brains and clinical data from 10,039 people reported a remarkably consistent Alzheimer's biological pattern in that group. Almost all APOE4 homozygotes in the pathology series showed Alzheimer's pathology; by age 65, nearly all in the biomarker analyses had abnormal cerebrospinal-fluid amyloid, and 75 percent had positive amyloid scans. The reported average age at symptom onset was 65.1 years, with a relatively narrow prediction interval.[2]

The authors argued that APOE4 homozygosity could be understood as a distinct genetic form of Alzheimer's disease, resembling other genetically defined forms in the consistency of its biological changes.[2] That is a substantial scientific claim. It is not the claim that every homozygote will notice symptoms on a particular birthday. Pathology, an abnormal biomarker, and disabling cognitive illness are different outcomes. An average onset age in a studied population is a description of that population, not an appointment made for a reader.

The distinction can feel evasive to someone seeking a straight answer. If almost everyone in a group develops the underlying biology, why resist treating the result as a forecast? Because a forecast has several possible objects. It may concern amyloid in cerebrospinal fluid, a positive scan, first detectable symptoms, a clinical diagnosis, or the loss of independence. The 2024 study's findings make the biological risk pattern unusually strong, but those endpoints do not collapse into one event.[2] Nor does a population average tell an individual how other illnesses, competing risks, or the limits of measurement will shape the years ahead.

There is another easily missed boundary: carrying one ε4 copy is not the same finding as carrying two. The 2024 argument about a distinct genetic form concerned homozygotes.[2] Family experience can intensify the urge to treat all APOE4 results alike, especially when a parent's illness supplies vivid evidence that a statistical summary cannot match. Yet a family history is not a laboratory result, and a laboratory result is not a family's clinical history. Each may be relevant in a clinician-mediated assessment; neither should be made to answer a question it was not designed to answer.

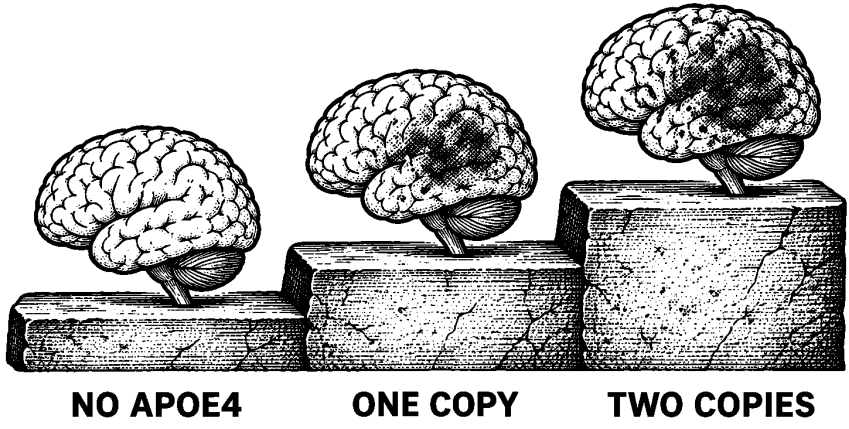


Figure 4. ARIA-E, brain swelling seen on MRI, becomes more common with each APOE4 copy among people treated with anti-amyloid antibodies, and homozygotes carry the highest risk. That is why both labels advise APOE4 testing before treatment. Overall ARIA-E rates were 12.6 percent with lecanemab in CLARITY AD and 24.0 percent with donanemab in TRAILBLAZER-ALZ 2 (14 percent at 24 weeks with donanemab's 2025 modified titration).

Risk information can also acquire an unwarranted sense of precision when it is paired with a proposed response. In October 2026, a meta-analysis combined results from three completed randomized multidomain lifestyle trials. FINGER, MAPT, and J-MINT, to ask whether APOE4 status changed cognitive-score responses. Participants were ages 60 to 85, but the trials defined elevated dementia risk in different ways, including risk scores, complaints or frailty, and mild cognitive impairment. The interaction between APOE4 status and intervention effect on global cognition met conventional statistical significance at 12 months, with $p = 0.039$; at 24 months it was borderline, with $p = 0.058$. The apparent difference related more to executive function than to memory or processing speed. These were cognitive outcomes, not measurements of dementia incidence.[3]

This is evidence worth following, not a validated instruction manual for an APOE4 carrier. On the series scale, B means a controlled human signal with limits; that is the narrow grade for the reported effect modification. The C headline for APOE4-specific lifestyle tailoring means that the broader claim, an established personal program to prevent dementia or slow decline in at-risk adults without dementia, remains no more than

observational or otherwise unconfirmed at the level readers care about. The trials tested multidomain programs in selected groups, not a sequence in which a person learns a genotype and receives a proven genotype-specific prescription.[3]

A second analysis illustrates why the word *subgroup* demands care. Among 442 participants in a biomarker subgroup of a three-year MIND diet trial, 134 carried APOE ε4. Higher baseline blood carotenoid levels among carriers were associated with better subsequent global cognitive trajectories; associations among noncarriers were weaker or not statistically significant. But carotenoid exposure was observed at baseline, not randomly assigned. The finding cannot establish that carotenoid supplements change cognition, still less that they prevent dementia in carriers.[4] A subgroup can generate a useful question while leaving the answer open.

The distinction between a biological response and a clinical one is just as sharp. In a randomized 24-month DHA trial involving 365 adults ages 55 to 80 without dementia, including 173 APOE ε4 carriers, DHA changed a cerebrospinal-fluid biochemical measure. The investigators found no evidence that this biochemical effect differed by APOE status, and they observed no treatment difference in cognition or brain volume over 24 months. Attrition was substantial: 38 percent of participants dropped out, mainly during the COVID-19 period.[5] It would be mistaken both to call the biochemical finding a cognitive success and to claim that this single trial settles every question about diet, lipids, and APOE.

At the more speculative end sits APOE gene therapy. A proposed program aimed to reduce APOE4 while delivering APOE2, but the company paused it in March 2026 while it was still preclinical; reported mouse results were not evidence of prevention in humans. The company said the pause was a prioritization decision rather than a response to program data.[6] The grade is Insufficient, meaning no human finding fits the series scale for a dementia-prevention claim. A plausible mechanism and an ambitious engineering plan do not constitute a treatment available to people with an APOE4 result.

There is a humane point beneath these distinctions. Learning a genotype does not create an obligation to reorganize every ordinary act around it. Nor does uncertainty erase the seriousness of the 2024 finding. Good evidence can make a risk more credible while still leaving the individual future unknown. The ethical question is not merely, “Can the result be

obtained?" It is also, "Which decision would this result clarify, and how confident are we that the proposed decision follows from the evidence?"

The Symptom Boundary

The May 2026 forum thread drew attention to people who might show subtle cognitive differences without dementia symptoms.[1] That phrasing sits near a consequential boundary. Research can study whether a blood marker predicts later impairment in people considered cognitively healthy. A diagnostic test cleared for clinical use, however, may have been evaluated for a different task: helping clinicians investigate symptoms already present. Prediction in an asymptomatic cohort and diagnostic assessment of a symptomatic patient are not interchangeable uses.

As of October 2026, the US-cleared Alzheimer's blood tests covered in this series are intended to aid evaluation of people with signs, symptoms, or complaints of cognitive decline; none is cleared to screen people without symptoms. The clearances include the Lumipulse p-tau217/amyloid ratio, an Elecsys p-tau181 test, and an Elecsys p-tau217 test, each with its own intended-use conditions.[7,8] The word *cleared* therefore needs its qualifying phrase. It does not mean that an apparently healthy adult has been offered a reliable preview of future dementia.

Consider what the first clearance actually established. In May 2025, the FDA cleared Fujirebio's Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio for adults 55 and older with signs and symptoms of cognitive decline. In the FDA-reviewed set of 499 plasma samples from cognitively impaired adults, 91.7 percent of positive blood-test results corresponded to amyloid plaques on the reference evaluation, while 97.3 percent of negative results corresponded to negative PET or cerebrospinal-fluid findings. Fewer than 20 percent of results were indeterminate. The FDA specified that the test was neither a screening tool nor a stand-alone diagnosis.[7]

Those percentages describe performance in the studied clinical setting, against evidence of amyloid pathology. They do not report the chance that a person without symptoms will develop dementia after receiving a positive result. If a test is moved into a population with a different prevalence of the condition it detects, the practical meaning of positive and negative results can change. Even within the intended population, amyloid evidence answers only part of the clinical question: it must be interpreted alongside symptoms and other information.[7,9]

A 2026 analysis of 303 patients with mild cognitive impairment or mild dementia offers a second view of both promise and limitation. In that symptomatic memory-clinic cohort, Elecsys plasma p-tau217 distinguished results against a cerebrospinal-fluid reference standard with an area under the curve of 0.93, compared with 0.87 for p-tau181. Using two thresholds gave high sensitivity at one end and high specificity at the other, but 27 percent of cases landed in an indeterminate interval. This study does not establish screening accuracy in people without symptoms.[10] The middle category is not an embarrassing flaw to be wished away; it is an acknowledgment that forcing every measurement into a confident yes or no can mislead.

As of October 2026, the FDA-cleared Elecsys pTau217 test is intended to aid assessment of amyloid pathology in people 55 and older with signs, symptoms, or complaints of cognitive decline in primary or specialty care. It reports positive, intermediate, or negative categories and is not a stand-alone test. Its manufacturer states that it has not been established for predicting dementia development or for monitoring treatment effects.[8] The presence of a test in primary care does not remove the symptom requirement. It changes where an appropriate evaluation may begin, not whom the test has been shown to benefit.

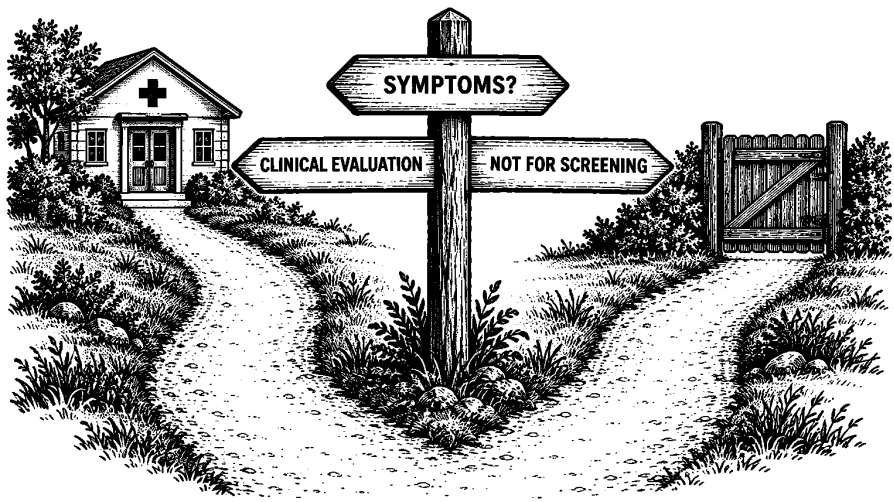


Figure 5. As of October 2026, the FDA-cleared Alzheimer's blood tests are intended for adults who already have symptoms, as one part of a clinical evaluation. None is cleared to screen people without symptoms.

The distinction from observational prediction matters because prediction studies are compelling reading. A cohort may find that participants with high p-tau217 are more likely to develop cognitive impairment years later; a 2026 report described an estimated five-year impairment risk of 38 percent among older adults with very high levels. That figure is an estimate for a defined research group, not a guarantee of symptoms for a particular person.[11] It also does not demonstrate that giving people their results, outside a research study, improves their health. A marker can predict an outcome without offering a proven intervention triggered by that marker.

The clinician-mediated path begins with the concern that brought a person to care: a change noticed by the patient, a relative, or someone else; its course; and other possible explanations. A blood biomarker can then contribute to an evaluation rather than replace one. The patient decision aid from the AGREED Dementia Group frames Alzheimer's blood tests for people with cognitive difficulties as part of a clinical assessment, not screening for people without symptoms.[12] That approach has a practical advantage even when the result is ambiguous: there is a person responsible for explaining what was measured, what remains uncertain, and what the next clinical question is.

At-home consumer testing reverses that order. Direct-to-consumer services have offered Alzheimer's biomarker packages, including p-tau217, without a doctor's order. Experts have warned that a biomarker result received without a cognitive evaluation or clinical context is not a stand-alone diagnosis.[13] The difficulty is not that every consumer result must be analytically false. It is that the recipient may be asked to carry the emotional and interpretive burden before anyone has established whether the test addresses a clinical problem. A numerical result can arrive quickly; a responsible account of its meaning takes longer.

This boundary should not be confused with refusing to assess a person who reports symptoms. The US Preventive Services Task Force found insufficient evidence to judge the benefits and harms of routine cognitive-impairment screening in community-dwelling adults 65 and older without recognized signs or symptoms. Its statement does not address evaluating people who have symptoms.[14] Similarly, a blood test intended to help assess symptomatic adults should not be promoted as a general screen merely because it is simpler than a scan. The difference is the question being asked of it.

For how to appraise a diagnostic claim separately from an outcome claim, see *The Longevity Operating System*, Chapters 2 and 15. The relevant outcome here is not just whether blood and scan results agree. It is whether testing people before symptoms, disclosing the result, and acting on it produces more benefit than harm. No published study has shown that Alzheimer's blood biomarker testing prevents dementia or slows cognitive decline.[7,8,10] Accuracy in one lane cannot silently be spent in another.

Why Antibody Risk Changes the Conversation

Genetic information has a different role when a person is already being assessed for a treatment with a known genotype-linked hazard. As of October 2026, lecanemab and donanemab are approved for eligible people with early symptomatic Alzheimer's disease and confirmed amyloid pathology; they are not approved as prevention for people without symptoms. Both carry boxed warnings concerning amyloid-related imaging abnormalities, or ARIA. APOE ε4 status matters in that treatment discussion because people with two ε4 copies have shown the highest ARIA risk. The status of these drugs does not turn a healthy APOE4 carrier into a treatment candidate.

ARIA is an imaging finding that may involve swelling or fluid accumulation, called ARIA-E, or microhemorrhages and related blood products, called ARIA-H. A 2026 review summarized ARIA-E rates across central antibody trials by genotype: 5.4 to 14.8 percent among noncarriers, 10.9 to 23.8 percent among people with one ε4 copy, and 32.6 to 41.1 percent among homozygotes. The review also identified baseline evidence of cerebral amyloid angiopathy and treatment factors as risk considerations. These ranges pool experience across trials; they are not a single drug's rate, an individual prognosis, or a substitute for a product's current label.[15]

The gradient is nonetheless large enough to change what informed discussion requires. If a proposed treatment has a hazard that differs substantially by genotype, learning APOE status can help explain the risk being considered. That is a narrower and more defensible use than testing an asymptomatic person to search for a drug that has not been approved to prevent the disease. It also places the genetic result in a setting where other information is already being assessed: symptoms, amyloid confirmation, imaging findings, eligibility, and the patient's understanding of potential benefit and harm.

This is why the same result can carry different ethical weight at different points in care. Before symptoms, an APOE4 finding may chiefly inform an uncertain forecast and family conversation. During assessment for an approved early-symptomatic treatment, it may bear directly on a known adverse-event risk. Neither setting makes genotype the sole decision-maker. The antibody review describes additional contributors to ARIA risk and differing monitoring frameworks, and it is a review rather than a new trial comparing strategies.[15] An allele count can sharpen a conversation without completing it.

It is also possible to overread the antibody evidence in the other direction. The fact that APOE4 homozygotes faced more ARIA-E in central trials does not establish that all such patients would experience ARIA, or that people without ε4 face none.[15] Trial averages describe groups exposed under study conditions. The clinical question concerns a particular approved treatment, its label, and an eligible person with symptomatic disease. Off-label use, including a prevention proposal for an asymptomatic person, is a question for a clinician; the evidence in this book does not support prescribing antibodies for dementia prevention.

Chapter 2 examined what treatment trials found about slowing decline in early symptomatic Alzheimer's disease. Here the point is consent rather than efficacy. A meaningful discussion of an antibody's possible benefit cannot omit a material, genotype-linked harm. Conversely, fear of that harm should not be used to turn APOE testing into routine population screening. A medical reason to know a genotype in one setting does not supply a medical reason to know it in every setting.

What Disclosure Can Cost

Tests are often described as if they produce information and nothing else. In practice, a result can change how someone interprets an ordinary lapse, talks with family, or imagines the future. A person who learns an APOE4 genotype may want relatives to know; those relatives may differ in whether they want the information themselves. A person who receives an Alzheimer's blood-biomarker result without symptoms may be left trying to reconcile a risk signal with a life that still feels unchanged. The strain does not prove that testing is wrong. It means disclosure is part of the intervention, not an administrative afterthought.

For APOE results, the possibility of insurance consequences deserves plain language. In the United States, the Genetic Information Nondiscrimination

Act, or GINA, prohibits genetic discrimination in health insurance and in employment for employers with at least 15 employees. GINA does not cover life, disability, or long-term-care insurance.[16] Saying only that "genetic information is protected" conceals the exception most likely to matter when someone is contemplating future care needs. Protections also have defined scopes; a general reassurance cannot stand in for the actual terms of a law or policy.

For genetic-test disclosure preparation, see Book One, *The Longevity Operating System*, Clinician Conversation Handbook. The preparation matters because the choice to learn is not always reversible in the ordinary sense. A result can be put away, but it cannot be unknown. It may also be disclosed in records or conversations that have their own consequences. This is an ethical issue even when the laboratory finding is correct and even when the person ultimately values knowing.

Blood biomarkers introduce a related but not identical problem. An APOE genotype concerns inherited risk; p-tau217 is measured as a marker associated with Alzheimer's biology and, in cleared uses, helps assess pathology in symptomatic adults.[7,8] Conflating the two under the phrase *Alzheimer's test* can produce an unintended disclosure. Someone may believe a consumer blood result establishes a diagnosis, while someone else may believe a genetic result demonstrates current disease. Neither inference follows merely from the label on a report.

The at-home model can make this confusion harder to repair. Some online or laboratory services offer Alzheimer's tests outside the clinician-led evaluation for which cleared tests are intended, and specialists have cautioned against testing people without symptoms outside research.[11,13] A report may present a threshold and a reference range without conveying the difference between confirming amyloid pathology in a symptomatic sample and predicting future impairment in an asymptomatic population. The numbers can look similar on a screen even when the questions behind them are fundamentally different.

There is a fairness question, too. A person who can obtain testing may not be able to obtain timely interpretation; a person who receives an indeterminate result may face another period of uncertainty rather than closure. The 2026 symptomatic memory-clinic analysis placed 27 percent of patients in its indeterminate interval under a two-threshold strategy.[10] That interval is scientifically honest, but its human burden should not be

hidden in a headline about accuracy. More sensitive tools can reveal more uncertain states as well as more clear ones.

The cost of disclosure is not only anxiety. It can be false reassurance. A negative biomarker result in an appropriate diagnostic assessment does not certify lifelong freedom from dementia, just as a positive result does not establish when symptoms will appear. The FDA's clearance language requires interpretation with other clinical information and rejects stand-alone diagnosis.[7] If a consumer treats either result as a final answer, testing may narrow attention precisely when a broader assessment is needed.

Nor should a risk result be made into a moral verdict about behavior. The 2026 lifestyle meta-analysis raises a developing question about whether APOE4 status modifies response on cognitive tests; it did not establish a genotype-specific program that prevents dementia.[3] A person who develops symptoms has not failed to live correctly, and a person with a favorable result has not earned immunity. Those statements are not polite qualifications to be appended after the science. They protect the science from being turned into blame.

The May 31 forum question remains understandable. A blood test that might register change before unmistakable symptoms would appeal to anyone who has seen diagnosis come late.[1] The familial APOE4 concern in the July material is understandable for a different reason: family memory can make an unknown future feel present. Neither concern is answered by telling people simply to know more or to avoid knowing. The answer depends on whether the information is suited to the question, whether its limits can be explained, and whether a decision genuinely becomes better informed.

As of October 2026, the firm boundary is that cleared Alzheimer's blood tests assist evaluation of symptomatic adults, not screening of people without symptoms.[7,8] The 2024 APOE4-homozygosity finding describes a powerful genetic pattern, not a certain personal timeline.[2] Genotype can be pertinent to ARIA risk before an approved antibody treatment for eligible early symptomatic disease, but it is not itself treatment advice.[15] Between those statements lies the ethical space this chapter has tried to keep open: a number may be consequential without being complete.

Part II: The Body Under the Brain

Chapter 4: A Starving Brain: Ketones, Diets, and Fuel



On July 4, 2023, a forum thread opened with a report that beta-hydroxybutyrate, a ketone body, might regulate protein solubility in the aging brain. The post described experiments in laboratory and mouse systems, then made the connection that gave the discussion its pull: beta-hydroxybutyrate can also serve as fuel.[1] That same day, John_Hemming asked, “I wonder what effects Ketone Ester has”.[2]

It was a small question with a large implied experiment. If an aging brain struggled to use its usual fuel, perhaps another fuel could help. If that fuel also changed how proteins behaved, perhaps it could do more than supply energy. None of those possibilities was absurd. But the thread had already crossed a boundary: from an observation about molecules and laboratory systems to a question about a product and, behind it, a hoped-for effect in people.

The boundary matters because a brain can take up ketones without a person becoming less likely to develop dementia. A scan can show a change in fuel use without showing a change in memory. Even a favorable cognitive-test result over weeks or months may not tell us what happens over years. This chapter follows that widening gap. It begins with the relatively direct question of whether ketones reach the brain, then moves through small cognition trials, a diet trial that combines two interventions, a longer trial with an unusually active comparison group, and finally the far less controlled world of dietary patterns.

The forum question deserves a fair hearing. Alzheimer’s disease is frightening partly because its course can feel impervious to ordinary

efforts. A fuel hypothesis offers a physical picture: supply something the brain can use, and perhaps the lights will stay on. The evidence is more specific, and less settled, than that picture.

A Fuel Hypothesis Meets a Brain

Ketones are often discussed as though they were a single treatment. In this literature, however, the word can refer to a measured blood molecule, a fuel entering the brain, a supplement, or the metabolic state sought through a diet. Those are related subjects, not interchangeable interventions. A ketone ester study does not test a ketogenic diet. A ketogenic diet does not test an isolated effect of fasting. And evidence that a brain uses an alternative substrate does not, by itself, establish that the substrate corrects the processes responsible for dementia.

The July forum post offered an especially appealing extension of the fuel story. It described beta-hydroxybutyrate as both an energy substrate and a participant in other cellular interactions, with protein-solubility findings drawn from in vitro, ex vivo, and mouse work.[1] The second possibility, that a metabolite might alter the behavior of proteins implicated in neurodegeneration, sounds closer to the disease itself than an energy boost does. Yet an experiment showing that proteins become less soluble cannot settle whether that change helps a living person think, function, or remain free of dementia.

A later reply in the same thread captured an unresolved question rather than smoothing it away. On December 4, 2024, AlexKChen asked, “So why is inducing insolubility a ‘good thing’?”[3] The distinction is not merely semantic. Keeping a harmful protein from participating in one reaction could be useful; making material harder to clear could present another problem. Laboratory results can help frame those questions. They cannot determine the net effect across a human brain over time.

The direct human measurements are narrower. An NIH-sponsored randomized, masked ketone-ester-versus-placebo study enrolled 99 cognitively intact adults aged 55 or older who had metabolic syndrome. Its planned intervention period was 28 days, and brain beta-hydroxybutyrate measured by magnetic resonance spectroscopy was among its metabolic measures. The study completed in June 2025, with results first posted to ClinicalTrials.gov in April 2026. It was a brain-metabolism study, not a trial of Alzheimer’s or mild cognitive impairment treatment; no published study has shown that this intervention prevents cognitive decline.[4] A

finding about brain fuel in those participants would answer something real, but not the forum's larger question about avoiding Alzheimer's disease.

A registry posting is not, by itself, an answer to the forum's question. Results for the ketone-ester study first appeared on ClinicalTrials.gov in April 2026, but its participants were cognitively intact and its planned intervention lasted 28 days.[4] Even a change in a brain-metabolism measure would not show whether the intervention prevents dementia years later. Nor would an unchanged measure settle every question about ketones and cognition. The trial's design defines what its results can address.

A second experiment comes closer to people with cognitive impairment while making attribution harder. In a six-month randomized pilot, 30 participants with mild cognitive impairment received either placebo or a combination of beta-hydroxybutyrate salt and nicotinamide riboside, an NAD+ precursor. PET-measured gray-matter ketone uptake increased 2.4-fold in the active group; white-matter uptake increased 3.1- to 3.6-fold across seven tracts.[5] Those are substantial changes in a measured pathway. They show that the intervention engaged the brain in a way imaging could detect.

The pilot also reported that myelin-density decline in parts of the fornix appeared in the placebo group but not the active group, and that processing-speed changes were associated with measures of white-matter ketone uptake and myelin. With 15 participants in each arm, and two active ingredients given together, the study cannot establish that ketones alone preserved white matter or produced a clinical benefit.[5] An association among measurements collected during a trial is not the same as a randomized comparison proving which ingredient caused a change. Nor is a processing-speed measure a dementia endpoint.

The fold changes deserve the same attention as the trial's size. A 2.4-fold increase in measured gray-matter ketone uptake describes the relative change in that measurement; it does not mean cognition improved 2.4-fold.[5] Imaging can detect an intervention's biological activity with a precision that everyday functioning does not offer. That sensitivity is valuable in an early trial, where investigators need to know whether an intervention reached its proposed target. It also creates an opening for an impressive image to carry a claim that the clinical observations have not yet earned.

This is the first recurring pattern in the chapter: evidence grows stronger for a narrow claim just as readers may be tempted to enlarge it. Brain

ketone uptake has been measured in human experiments.[4,5] That finding supports the proposition that ketones can reach and be used by the brain. It does not show that adding ketones prevents dementia in someone who currently thinks clearly, or that changing uptake slows Alzheimer's disease once symptoms appear.[4,5] The distance between those claims is where much of the marketing language, and much of the sincere hope, resides.

Another forum discussion illustrates how easily a measured metabolite can be mistaken for a lever. In December 2024, John_Hemming posted an excerpt about circulating ketone bodies and other energy metabolites in relation to cognitive decline and dementia risk.[6] Such an association asks whether people with different measured levels also have different outcomes. It does not tell us what would happen if investigators changed one metabolite while leaving the rest of a person's health unchanged. Illness, diet, activity, and the body's response to disease can all affect what circulates in blood. A blood measurement may be a clue about a system rather than a handle by which to move it.

For the same reason, "feeding the brain" is not a sufficient definition of success. The brain is not merely an engine short of fuel. A useful prevention study would have to show a difference in outcomes that matter to people, over a period appropriate to the claim. When trials instead measure a metabolite, an image, or a brief cognitive change, the results belong to those endpoints. That discipline does not dismiss mechanism; it gives mechanism a proper place in the evidence chain.

Ketones in Small Human Trials

By April 2026, a systematic review had gathered 38 studies of exogenous ketone bodies across health and disease, comprising 41 protocols and 1,602 participants. Twenty-nine protocols involving 1,117 participants entered its meta-analysis. The pooled cognitive-test effect favored exogenous ketones, with a standardized mean difference of 0.29 and a 95% confidence interval of 0.16 to 0.41. Heterogeneity was high: I^2 was 91%.[7] On its face, this is a small favorable signal, not a null result. It is also a signal drawn from protocols that differed enough for their results to vary considerably.

For the subgroup of greatest interest here, participants with mild cognitive impairment or Alzheimer's disease, the pooled effect was smaller, a standardized mean difference of 0.15. Differences by population or supplement type were not statistically significant, and the reviewers noted limited long-term evidence. Some coauthors reported commercial

interests.[7] The conflict disclosures do not erase the data. They add a reason to read claims about particular products with care, especially when the pooled estimate is sometimes presented as if it established a durable benefit for one formulation in one disease.

A standardized mean difference helps combine unlike cognitive tests. It does not tell a family how many meaningful months of independent living were gained, whether a diagnosis was delayed, or whether everyday memory improved enough to notice. High heterogeneity also changes how the average should be heard. If studies differ substantially, the pooled number is not a dependable prediction for every population or intervention. The subgroup estimate for MCI and Alzheimer's disease is relevant enough to keep studying; it is too small and uncertain to carry a prevention claim.[7]

Nor should the confidence interval around the pooled estimate be mistaken for a complete description of uncertainty. It describes uncertainty around an average calculated from the included protocols; it does not remove the substantial variation among their results.[7] A future study in a defined group could find a different effect without contradicting the existence of that pooled average. This matters most when someone moves from "exogenous ketones, across studies" to "this product, for a person at risk of dementia." The second statement demands evidence far more specific than the first.

The forum's MCT-oil discussion shows why those distinctions have practical force. On January 12, 2024, L_H wrote that the interest was in "the long term benefits," then reasoned from a possible energy benefit in Alzheimer's disease toward prevention in healthy brains.[8] The post put into ordinary language the leap that a trial program would need to test. Short-term cognitive performance in mixed study populations, clinical effects in people already impaired, and prevention in people without impairment are three different questions. A favorable answer to one cannot be loaned to the others.

The same thread included a more grounded question. ActivePassenger asked, "Does MCT, being a saturated fat, raise ApoB?"[9] The studies discussed here do not quantify product-specific long-term lipid effects, so they cannot answer that question for MCT oil or settle how a particular formulation changes risk.[4,5,7,10] Still, the question exposes a blind spot in the single-organ story. A proposed brain benefit would need to be considered alongside effects elsewhere in the body. Digestive effects and changes in blood lipids also matter when interpreting whether an

intervention can be sustained, although the small cognition studies do not establish a long-term balance of benefits and harms for dementia prevention.[7]

One might group MCT oil and ketone esters together because both sit under the ketone hypothesis. The grouping is useful for asking whether the hypothesis has a human cognitive signal; it is less useful for claiming that either specific product works. The 2026 review found no statistically significant difference by supplement type. That is not proof that all types are equivalent. Given the variation among studies and the limited long-term evidence, it means the available comparisons did not reliably separate them.[7]

The series headline grade for MCT oil and ketone esters is C for preventing dementia or slowing decline in at-risk adults without dementia. On this scale, C denotes observational or uncontrolled human evidence for the stated headline claim; the grade does not deny that small controlled human studies provide a stronger, narrower cognitive-test signal. The pooled effect is modest, and neither its average across mixed populations nor its MCI/Alzheimer's subgroup establishes prevention.[7] The grade attaches to what a reader most wants to know, not to the most promising measurement in the file.

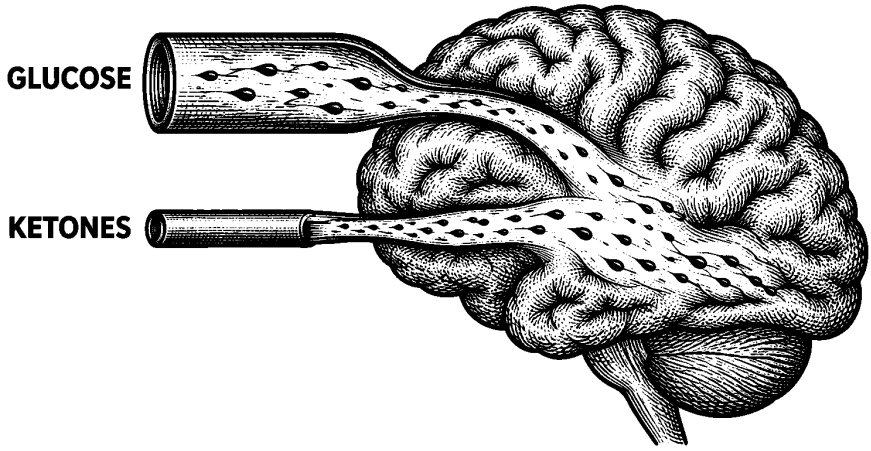


Figure 6. The fuel-switch idea: in Alzheimer's disease the brain's uptake of glucose falls, while its uptake of ketones appears relatively preserved. Small trials of ketogenic diets, MCT oil and ketone drinks show modest effects at most on cognitive tests, and no trial has shown that they prevent dementia.

A useful way to read Figure 6 is as a set of questions rather than a pipeline that must end in success. Did an intervention change circulating ketones? Did those ketones reach the brain? Did a cognitive measure change relative to a control? Did functioning or disease risk change over a meaningful period? An affirmative result at an early step creates a reason to test the next one. It does not answer it.

That principle becomes more demanding when the intervention ceases to be a defined product and becomes an eating pattern. Food changes many exposures at once. People may replace some foods with others, change total energy intake, or alter body weight. Those changes may be part of an intervention’s real-world effect, but they make it difficult to credit an observed outcome to ketones specifically. The next trial reached further toward a clinical population while combining precisely the elements a reader might wish to separate.

The Diet Against Its Control

A randomized trial published in September 2026 enrolled 60 people aged 55 to 85 with early-to-mid-stage Alzheimer's disease. For six months, one group received a plant-rich ketogenic diet combined with intermittent fasting plus standard care; the other received standard care alone. Outcome assessors were blinded. Mean Mini-Mental State Examination scores changed by +0.9 points in the intervention group and −1.5 points in the control group, and the between-group difference in cognitive change scores was statistically significant. A Reliable Change Index classified cognition as stable in 93% of intervention participants versus 70% of controls.[10]

The mean changes put the statistical result on a more recognizable scale: the groups' average changes were 2.4 MMSE points apart over six months.[10] That arithmetic describes a difference between group averages, not an individual participant's expected improvement. Likewise, 93% versus 70% is a 23-percentage-point difference in the trial's *stable cognition* classification; it is not a 23% reduction in dementia risk.[10] These distinctions preserve the finding while preventing two attractive numbers from being recast as outcomes the study did not measure.

That is a controlled result in people with Alzheimer's disease, not merely a biomarker. Its limitations should be stated without pretending the result vanished. The trial was small and lasted six months. More importantly for interpretation, its intervention was a package: plant-rich food choices, a ketogenic diet, and intermittent fasting. The comparison was standard care alone, not the same diet without fasting, the same fasting pattern without ketogenic eating, or a matched dietary program with a different composition. The trial therefore cannot identify fasting as the active ingredient, or ketones as the cause of the observed difference.[10]

A package can still be worth testing. In daily life, dietary interventions are often packages. But the question answered by a package trial is whether that package performed differently from its particular control over the period observed. It is not a license to select the component that best fits a preexisting theory. If the plant-rich foods were central, attributing the result to fasting would miss them. If changes in total eating or caregiver support contributed, a ketone-only account would also be incomplete. These are possibilities raised by the design, not findings demonstrated by the trial.

The result is narrower in another direction: the participants already had Alzheimer's disease.[10] Even a well-replicated treatment effect in

symptomatic people would not automatically show that the same approach prevents dementia in cognitively intact adults. The populations enter a study with different biology, constraints, and outcomes available for measurement. Here, a single small trial of a combined intervention cannot establish either a general Alzheimer's treatment or a prevention benefit.[10]

For a ketogenic diet, the headline grade is C for preventing dementia or slowing cognitive decline in at-risk adults without dementia. Small, short controlled studies in MCI or Alzheimer's disease offer a stronger but narrower human signal; this six-month combined-intervention trial adds an outcome in symptomatic disease without isolating ketogenic eating.[10] C is not a judgment that dietary change is useless. It is a statement about the mismatch between the evidence and the prevention claim.

The contrast with the MIND diet trial is instructive because its control group was not doing nothing. Published in 2023, that trial randomized 604 cognitively unimpaired adults aged 65 or older who had a family history of dementia, overweight or obesity, and a suboptimal diet. One group followed a MIND-diet intervention; the control group also received mild caloric restriction. Over three years, global cognition improved in both groups. The between-group difference was 0.035 standardized units, with a 95% confidence interval from −0.022 to 0.092 and a P value of 0.23. Brain MRI changes were similar.[11]

In August 2023, a forum discussion of the trial focused on the comparison itself: the opening post described intensive counseling around the MIND diet and noted that both groups had mild caloric restriction.[12] That observation gets to the heart of the result. The trial did not ask whether a MIND dietary program beats no attention to food. It asked whether that program produces an additional cognitive benefit over an active comparison that also changed eating. The answer, on the measured global-cognition and MRI outcomes, was no significant added difference over three years.[11]

An active control can make a trial harder for a favored intervention to win, but that is not a defect to be waved away. It can make the result more relevant to the choice actually at issue: whether one organized approach adds something beyond another credible dietary change. If both groups improved, the shared improvement cannot be assigned specifically to the MIND diet. Nor can the trial prove that caloric restriction caused it; aging, repeated testing, participation, and other shared features would require

their own comparisons to separate. The trial's firmest conclusion is the between-group one.[11]

This is the meaning of B-null for the MIND diet against the tested active control: controlled human evidence found no effect on the endpoint tested relative to that comparison.[11] The headline prevention grade remains C, because the trial measured cognitive change rather than dementia incidence, and other human evidence includes associations that do not establish causality.[11,13] B-null should not be stretched into "the MIND diet is no better than eating poorly," a comparison the trial did not make. C should not be stretched into "the MIND diet prevents Alzheimer's," an outcome the available evidence does not establish.

These two randomized studies pull attention toward an often-neglected word in a trial report: *versus*. The ketogenic-diet-and-fasting package looked better than standard care alone over six months in a small symptomatic group.[10] The MIND diet did not add a statistically significant cognitive benefit over an active calorie-restricted dietary comparison across three years in cognitively unimpaired adults.[11] Different populations, durations, interventions, and controls prevent a simple ranking. A reader who overlooks the control group can make either study say much more than it did.

For the broader questions of general food quality, energy balance, and muscle, see Book One, *The Longevity Operating System*, Chapter 6.

Patterns, Processing, and Missing Outcomes

As trials grow less direct, cohort studies supply scale and time. A prospective analysis published in March 2026 drew on repeated dietary assessments from 86,740 women in the Nurses' Health Study and 43,500 men in the Health Professionals Follow-Up Study, with follow-up reaching up to 43 years. Compared with the lowest adherence category, the highest Mediterranean-diet category was associated with 21% lower dementia risk, a hazard ratio of 0.79. The highest MIND-diet category was associated with 14% lower risk, a hazard ratio of 0.86.[13] These are not tiny studies or momentary observations. They also are not randomized assignments to a diet.

Those percentages are relative comparisons between the highest and lowest adherence categories, not absolute probabilities that an individual will develop dementia.[13] Without a baseline risk specified for the relevant group

and period, "21% lower risk" cannot responsibly be translated into a number of diagnoses avoided. Nor does the comparison describe what happens when someone makes a modest change in an already adequate diet. The cohort result is informative about differences observed across dietary categories; it is not a forecast for any particular change in a grocery basket.

The MIND association does not overturn the trial's null between-group cognitive finding. The cohort followed people whose eating patterns differed alongside many other features of their lives; the trial compared assigned interventions under its own conditions for three years.[11,13] Each design has strengths. Long follow-up can capture diagnoses that a shorter trial may miss. Randomization can make groups more comparable at the start. Neither strength turns one study into a direct answer to the other study's question.

A second MIND cohort result helps show why intermediate outcomes remain tempting. Among 1,647 Framingham Offspring participants followed for a median of 12.3 years, each three-point higher MIND score was associated with 0.279 cubic centimeters per year slower decline in total gray-matter volume, an estimate the authors expressed as 20.1% attenuation of age-related change.[14] Brain structure feels more concrete than a food questionnaire. Yet participants were not assigned a MIND score at random, and slower measured volume loss is not itself proof of fewer dementia cases.[14] The study supplies a plausible link for further work, not a completed causal chain.

Plant-based eating requires similar care with definitions. In a multiethnic cohort analysis of 92,849 participants with baseline diet data, the highest versus lowest overall plant-based diet score was associated with 12% lower risk of Alzheimer disease and related dementias. For a *healthful* plant-based score, the association was 7% lower; for an *unhealthful* plant-based score, it was 6% higher. The cohort included African American, Japanese American, Latino, Native Hawaiian, and White adults, and associations were generally similar by APOE ε4 carrier status.[15] The divergent scores make "plant-based" too blunt a label to carry the whole result.

There is a causal trap even in that more discriminating account. People who consistently choose foods scored as healthful may differ in education, access to care, smoking, physical activity, income, or other factors that are difficult to measure perfectly. Dietary questionnaires also compress

complicated, changing behavior into categories. Statistical adjustment can address measured differences, not guarantee the removal of every relevant difference. The multiethnic study's observational design does not establish that switching a person to a higher-scoring pattern would produce the reported risk change.[15]

As of October 2026, the headline grade for Mediterranean and plant-based patterns is C for dementia prevention: these are human observational associations, not randomized proof of a prevention effect.[13,15] That grade does not imply the patterns are identical, or that the associations should be ignored. It preserves the distinction between seeing a difference among people and producing a difference by changing what they eat.

A forum post from August 25, 2026, summarized a review of whole-food dietary patterns and cognitive outcomes, emphasizing patterns rather than isolated nutrients.[16] There is an understandable appeal to that framing. Meals are consumed as meals, and replacing one pattern changes more than a single molecule. But "the pattern" is also harder to define precisely, harder to keep stable for years, and harder to compare with a control that changes nothing else. The closer research gets to ordinary eating, the further it often moves from an isolated fuel experiment.

Ultra-processed food offers a related problem from the opposite direction. A 2026 systematic review found five observational studies examining cognitive performance, cognitive decline, dementia risk, or cognitive-impairment risk. The studies reported adverse associations in some population subgroups or ultra-processed-food categories, but they did not all find a significant overall association. The review searched literature through October 2024, and its authors cautioned that the evidence base was small and outcomes varied.[17] That supports a careful description of an observed concern, not a claim that the review has identified a particular dementia-causing food.

"Eat less ultra-processed food" can sound like a single intervention, but the missing half of the sentence is what replaces it. A substitution can change energy intake, nutrient composition, cost, convenience, and the likelihood that an eating pattern can be maintained. Observational associations between processing categories and cognition cannot determine that any one specific substitute prevents dementia.[17] Even if an observed association proves meaningful, the mechanism might not be the category label itself. A claim about what to remove is incomplete until a study also makes clear what took its place.

There is no need to choose between treating food as nothing but fuel and treating every favorable association as prevention. The ketone experiments offer evidence about uptake and small cognitive signals; the dietary trials test particular packages against particular controls; cohorts place real-world patterns beside long-term outcomes.[4,5,7,10,11,13,15] They are complementary forms of inquiry precisely because they answer different questions. Trouble begins when the strongest sentence from each is assembled into a single promise that none of them tested.

The Fasting Gap

Fasting entered the strongest-looking dietary result in this chapter as one part of a combination. In the six-month Alzheimer's trial, participants assigned to the intervention received both a plant-rich ketogenic diet and intermittent fasting. Their cognitive change compared favorably with standard care alone.[10] It would be easy to describe the finding as evidence that fasting "works for the brain," particularly when fasting already has a persuasive metabolic story attached to it. The design does not permit that conclusion.

To identify an independent fasting effect, a comparison would need to separate fasting from the other changes made at the same time. This trial did not.[10] That does not mean fasting had no role; it means the contribution is unknown. A component can be helpful, irrelevant, or even offset by other parts of a successful package without the package comparison revealing which is true. The more ingredients a dietary intervention contains, the more restraint its interpretation requires.

Time-restricted eating raises an additional distinction. A proposed change in when food is eaten is not automatically a change in what is eaten, how much is eaten, or what happens in the brain. Nor does a metabolic response establish a cognitive outcome. The permitted human evidence here does not establish that time-restricted eating or intermittent fasting prevents dementia or slows cognitive decline in at-risk adults without dementia. The ketogenic-diet-and-fasting study concerned people who already had Alzheimer's disease and did not isolate fasting.[10]

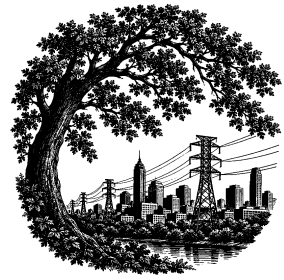
For time-restricted eating and fasting, the headline grade is Insufficient for brain outcomes. On the series scale, Insufficient means that the available evidence does not fit the stated prevention claim; it is not a verdict that no future trial could find an effect. Particular caution is warranted in diabetes, where changes in food intake can interact with glucose-lowering treatment,

and in frailty, where maintaining adequate nourishment and muscle is already difficult. Those concerns belong in the interpretation of a fasting proposal even when the hoped-for endpoint is the brain.

The chapter began with a molecule that could be measured and a question about what it might do. The answer now available is neither a dismissal nor a prescription. Ketones can be studied entering the brain, and a 2026 review found a small pooled cognitive-test advantage for exogenous ketones across varied human studies.[4,5,7] A small combined diet-and-fasting trial reported a favorable six-month cognitive difference in people with Alzheimer's disease.[10] Longer dietary observations associate some patterns with lower dementia risk, while the three-year MIND trial found no significant added cognitive benefit over its active control.[11,13,15]

Those findings leave the original appeal intact as a research question and incomplete as a prevention claim. A starving-brain metaphor points toward metabolism; it does not identify a single missing fuel or show that supplying it keeps Alzheimer's disease away. The most useful distinction is the least glamorous one: between a brain that takes up something new and a person whose future has been changed.

Chapter 5: Type 3 Diabetes



The temptation was to make one drug stand for the whole theory. If Alzheimer's disease was, in some meaningful sense, "type 3 diabetes," then perhaps metformin, the familiar diabetes drug already under discussion in the longevity forum, could protect the brain long before memory failed. That was the attraction of the argument, and also the first place it began to come apart.

The forum did not agree about metformin. Some members saw decades of clinical use and an accumulating set of dementia associations as reasons to take its preventive possibilities seriously. Others asked whether findings in people with established type 2 diabetes said anything about people without it, or whether a possible benefit might come at the expense of gains from exercise training. The disagreement was not between people who cared about evidence and people who did not. It was about which evidence answered the question they most wanted answered.

A physician posting in the community had offered the wider idea: impaired insulin signaling and glucose use in the brain might contribute to late-life Alzheimer's disease. His formulation gave the discussion a mechanism, rather than merely a drug to argue over. But a mechanism can support several competing predictions. If brain insulin signaling is impaired, would a drug that improves glucose regulation elsewhere help? Would insulin delivered to the brain help more directly? Would good diabetes care change long-term risk without reversing changes in an already symptomatic brain? Each question calls for a different test.

The newer studies make the argument more interesting, not tidier. A clinical trial tested insulin delivered toward the brain. A decades-long follow-up returned to people originally randomized in a

diabetes-prevention study. Large health-record cohorts compared diabetes drugs and measured glucose in relation to later dementia. Their results do not add up to a prescription. They show how much can hide inside the phrase *type 3 diabetes*.

The Metaphor's Useful Limit

"Type 3 diabetes" is a hypothesis-bearing metaphor, not a recognized diagnosis of Alzheimer's disease. It proposes that disrupted insulin signaling and glucose metabolism in the brain may contribute to its pathology; it does not establish that Alzheimer's is simply diabetes in another organ, or that a diabetes drug prevents it. A 2026 review of Alzheimer's treatments treats metabolic mechanisms as subjects of investigation alongside other disease processes, rather than as a settled replacement for them.[1]

The metaphor earns its place because insulin does more in the brain than regulate a blood-sugar reading. It participates in signaling related to synapses, metabolism, inflammation, and vascular function. Yet most glucose entering the adult brain does not require insulin to open a cellular door. The transporters that supply much of the brain differ from the familiar insulin-responsive picture drawn from muscle and fat. "The brain cannot get glucose because it is insulin resistant" is therefore too blunt an account of what researchers are testing.

Even the phrase *brain insulin resistance* can refer to several partly overlapping problems. A receptor may respond differently; signals inside a cell may change; blood vessels and inflammation may alter the local environment; or a region may use less glucose because disease has already damaged the cells that used to consume it. A brain scan showing reduced glucose use cannot, by itself, settle which process came first. Amyloid and tau do not disappear from the account merely because metabolism is involved. Nor does an association between type 2 diabetes and dementia prove that one molecular pathway explains every case.

That uncertainty matters most when the metaphor moves from explanation to intervention. Blood glucose, brain glucose use, and neuronal insulin signaling are related, but they are not interchangeable measurements. Improving one may not repair another. Nor would a result in people with years of type 2 diabetes automatically transfer to an adult without diabetes who is worried about future memory loss. Treating a diagnosed metabolic

disease can reduce exposure to harm without establishing that the same drug benefits a person who does not have that disease.

There is also more than one route from diabetes to cognitive impairment. Vascular injury is an obvious candidate: damage to small and large blood vessels need not operate through precisely the same pathway as Alzheimer's pathology. Illness severity, kidney and cardiovascular disease, and the ability to maintain ordinary care can shape both treatment and recorded dementia risk. A broad label that joins these routes may help a community notice a neglected question. It becomes less helpful if it makes all answers sound like confirmation of the same theory.

This is a problem of what a theory could prove wrong. If a drug improves a metabolic marker but cognition does not change, a supporter might say the treatment came too late. If cognition changes without the predicted marker changing, the same supporter might credit a different metabolic pathway. Either explanation could eventually be tested. Used only after a disappointing result, however, it leaves the original claim untouched no matter what happens. The useful version of "type 3 diabetes" makes predictions narrow enough to survive a fair test, or fail one.

The forum's metformin debate exposed that weakness early. Observational work in people with type 2 diabetes had associated longer metformin use with lower dementia incidence. A Taiwanese study discussed in the July account reported a gradient across cumulative exposure; a later meta-analysis pooled twenty cohorts and 3.46 million participants, estimating a lower observed dementia hazard among metformin users, while reporting very high disagreement across studies. Those were reasons to investigate, not proof that metformin caused the difference.

Cumulative treatment has a second meaning besides drug exposure: time spent alive, observed, and able to continue treatment. A person who develops serious illness may have a drug stopped; someone becoming frail or cognitively impaired may take it less consistently. Kidney disease can affect whether metformin remains suitable. The longer a comparison runs, the more these differences can accumulate. A smooth-looking exposure gradient may reflect some drug effect, some selection of healthier continuing users, or both.

The members disagreeing about metformin were thus arguing over a real gap. Evidence from diagnosed diabetes could not tell them whether non-diabetic prevention worked. The exercise question made the gap sharper: trials discussed in the July account found that metformin

attenuated some gains from supervised aerobic or resistance training in older adults. That finding did not show that metformin causes dementia, or that every potential benefit is outweighed. It did mean that a supposed preventive gain could not be considered in isolation from another activity with demonstrated health benefits. For the fuller account of that tradeoff, see Book Two, *mTOR, Metabolism, and Muscle*, Chapter 11, "Metformin and the Exercise Paradox."

A metaphor should produce tests capable of disappointing its supporters. The direct test of insulin delivered toward the brain did just that.

Insulin Delivered to the Brain

If impaired brain insulin signaling contributes to cognitive symptoms, intranasal insulin offers a more direct experiment than comparing people who did or did not take a diabetes tablet. The premise was to affect central signaling while measuring whether patients actually did better. A favorable laboratory story would not be enough; memory and other clinical outcomes had to move.

The SNIFF trial randomized 289 adults with mild cognitive impairment or mild Alzheimer's dementia to intranasal insulin or placebo for twelve months. Its initial delivery device proved unreliable, an unusually consequential practical problem for a trial whose proposed effect depends on delivery. The principal analysis therefore used the 240 participants in the second-device population. On its primary cognitive measure, ADAS-Cog-12, the between-group difference in change was 0.0258 points, with a 95 percent confidence interval from −1.771 to 1.822 and a P value of.98. Other measured clinical and cerebrospinal-fluid outcomes did not differ either. No clinically important adverse events were attributed to treatment.[2]

The device problem deserves neither concealment nor unlimited explanatory power. It narrows confidence in what can be said about the first device. It does not turn the second-device result into an unobserved success. In the population and period used for the main analysis, the trial did not find a benefit on the clinical and CSF endpoints it tested. That is B-null evidence: a controlled human test showing no effect on those endpoints, with the usual limits of a particular intervention, group, and duration.[2]

The confidence interval gives a more useful account than the P value alone. A point estimate close to zero describes what the trial observed; the interval describes the range of differences compatible with its data under the statistical model. It does not prove that every conceivable benefit is impossible. But reading the device failure as though it concealed a demonstrated clinical benefit would ask the trial to say the opposite of what its principal analysis found.[2]

SNIFF did not randomize healthy adults for decades and count new cases of dementia. It therefore cannot show that every possible insulin-based preventive approach will fail. Equally, a hypothesis about long-term prevention cannot be used to erase a null result in people who already had measurable impairment. These are different claims. Keeping them separate is what allows an appealing biological idea to remain testable rather than becoming immune to disappointing trials.

The distinction between delivery and disease mechanism cuts both ways. A clinical null can arise because the theory is incomplete, because the intervention does not change the relevant process sufficiently, because treatment begins too late, or because a measured endpoint misses an effect. Those possibilities are legitimate questions for further research. They are not findings of benefit. The SNIFF result places a boundary around a specific claim: intranasal insulin, as tested there, did not improve the measured outcomes over twelve months.[2]

There is a more general lesson in the trial's unglamorous device failure. A mechanism on paper still needs a workable intervention in people. The path from insulin signaling in a cell to cognition in someone living with impairment passes through delivery, exposure, competing pathology, and the reliability of the outcome measure. Each step can fail independently. That is why a null trial can be informative even when it cannot settle the entire metaphor.

Metformin presents almost the reverse situation. It is a widely used clinical drug, so the obstacle is not whether people can take it for an established indication. The difficult question is whether an apparent cognitive benefit belongs to the drug, to the people who remained available to study decades later, or to chance in a small number of dementia cases.

Metformin Decades Later

The Diabetes Prevention Program began with a stronger starting point than an ordinary drug-user cohort: participants were originally randomized to metformin, placebo, or an intensive lifestyle intervention in 1996–1999. In 2022–2024, investigators assessed cognitive impairment syndromes in 1,483 participants in its long-term follow-up, the Diabetes Prevention Program Outcomes Study. Their mean or median reported age was about 74, and the original metformin group had accumulated an average of 15.5 years of metformin exposure.[3,4]

The first report, a June 2026 conference abstract, drew attention with substantially lower odds of dementia among those originally assigned to metformin than among those assigned to placebo or intensive lifestyle intervention. An August preprint reported adjusted odds ratios of 0.40 against placebo and 0.38 against lifestyle for that dementia comparison. The original assignment matters: unlike a conventional comparison of continuing users and non-users, it was decided before the later cognitive outcomes were known.[3,4]

Those odds ratios are striking, but they are not absolute risk reductions. An odds ratio of 0.40 compares the odds in two groups; it does not mean that forty percent of participants developed dementia, or that treatment prevented dementia in sixty percent of the people assigned to it. Without the relevant event counts and risks alongside the estimate, a reader cannot translate it into a number of dementia cases avoided among a hundred comparable people. That distinction matters especially when the reported number of dementia cases is limited.[4]

But the headline is narrower than "metformin preserved cognition." In the preprint, the overall distribution of cognitive impairment syndromes did not differ significantly by original treatment group. Dementia case numbers were limited, and the authors called for longer follow-up to confirm the finding. The conference abstract and preprint are reports of the same long-running research, not independent replications of its dementia signal. As of October 2026, the detailed report cited here remained a preprint.[3,4]

Randomization gives the original comparison an advantage; it does not make everyone randomized three decades earlier equally observable in late life. These cognitive assessments describe participants who survived and were available for evaluation in 2022–2024. If assignment, later health, continued participation, and survival relate to one another, the assessed

group can differ from the group originally randomized. Long-term exposure also ceased to be simply "the drug assigned at baseline": treatment and health evolved over many years. The survivor-analysis limitation does not disprove the reported dementia association. It means the old randomization cannot, by itself, remove every selection problem from this late-life subset.

There is another easily missed distinction. The study's favorable comparison concerns later *prevalent* dementia among assessed participants, not a cleanly observed sequence in which every original participant was followed to a first dementia diagnosis under unchanged treatment. Dementia can prevent participation as well as be counted during it. Death can preclude a diagnosis. For a condition that becomes more common with age, who remains in a late assessment is part of the interpretation, not a footnote.

The comparison with intensive lifestyle intervention is particularly easy to overread. Lower dementia odds in the original metformin group do not establish that metformin is better for a person's health than physical activity or other elements of diabetes-prevention care. The reported endpoint was later dementia prevalence in an assessed subset, while the overall distribution of cognitive impairment syndromes did not differ significantly across groups. Turning that narrow contrast into an argument against lifestyle measures would give one late outcome authority over questions it was not designed to settle.[3,4]

The finding nevertheless deserves more attention than a casual observational association. Original randomization reduces the likelihood that doctors selected metformin because its recipients were healthier at the outset. Decades of follow-up address a question a one-year study could not. A sizable difference in later dementia odds is worth testing against further cases and careful analysis of participation. Skepticism should not flatten a potentially informative result into "just correlation"; enthusiasm should not promote one limited secondary outcome into settled prevention.

This is why the evidence grades need two lanes. For the headline claim, metformin for dementia prevention in people without diabetes, the grade is C. C denotes observational or otherwise uncontrolled human support for that claim, not an established preventive effect. For the narrower DPPOS finding on overall cognition, B-null describes the lack of a significant difference across the overall distribution of cognitive impairment syndromes in a study rooted in random assignment. It does not negate the

narrower dementia signal, and the dementia signal does not convert the overall result into a positive trial.[3,4]

DPP participants were originally enrolled for diabetes prevention, which makes the study especially relevant to the forum's question about use before diagnosed diabetes. Yet it still cannot straightforwardly answer whether an otherwise healthy adult with normal glucose regulation would gain cognitive protection by starting metformin. The late-assessed population was selected by survival and participation, the dementia cases were few, and the report has not established a broad cognitive benefit. Extending its result to every non-diabetic adult would require another inference on top of an already qualified finding.

As of October 2026, MET-FINGER, which studies a lifestyle-and-metformin approach, was ongoing without reported results.[5] As of October 2026, the proposed TAME metformin aging trial had not launched, had no ClinicalTrials.gov registration or enrollment, and was described by its sponsor as seeking funding.[6] Neither an ongoing study nor an unlaunched one can fill a dementia-prevention evidence gap by reputation alone.

The forum's disagreement therefore survives the update, though in a more precise form. Its cautious members were right that diabetes cohorts could not settle non-diabetic use. Those drawn to metformin's long history were right that it was a serious enough candidate to study rather than dismiss from a mechanistic sketch. DPPOS adds a provocative, limited dementia finding and a null overall cognitive comparison. It does not award either side a simple victory.

For the broader evidence on metabolic drugs, see Book One, *The Longevity Operating System*, Chapter 14, "Metabolic Drugs."

Diabetes Cohorts and Their Confounders

Metformin is only one way to test the metabolic idea. SGLT2 inhibitors, drugs used for established diabetes and other labeled conditions, have generated dementia associations of their own. If several classes appear protective, that could suggest that better metabolic or cardiovascular health matters more than one favored molecular mechanism. It could also mean that the patients receiving each class differ in ways records do not fully capture.

A South Korean study used records from eleven hospitals and compared new users of SGLT2 inhibitors with users of thiazolidinediones who had type 2 diabetes and were at least 40 years old. After matching, its dementia analysis included 25,111 pairs. SGLT2 use was associated with a lower recorded dementia risk, hazard ratio 0.66 with a 95 percent confidence interval of 0.45 to 0.98; an Alzheimer's analysis using 25,237 pairs reported a hazard ratio of 0.54, with a 95 percent confidence interval of 0.35 to 0.83. Matching was limited primarily to sex, leaving substantial scope for residual differences between groups.[7]

A hazard ratio is another relative comparison, not a count of people spared dementia. The Korean study's estimate of 0.66 for dementia describes the relative rate observed over follow-up under its comparison; by itself it does not tell a reader the absolute difference in diagnoses. Its confidence interval extends almost to 1.0, where the groups would have the same rate under that model. The Alzheimer's estimate is lower, but it comes from the same observational setting and faces the same treatment-selection problem.[7]

Using another active diabetes drug as the comparator is better suited to this question than comparing treated patients with people taking no drug at all. Both groups had entered care and received treatment. Still, the reason a clinician selects an SGLT2 inhibitor rather than a thiazolidinedione may be linked to cardiovascular history, kidney function, frailty, other medications, or factors absent from the matching. An active comparator reduces some distortions; it does not randomize the choice.

The grade for SGLT2 inhibitors and dementia associations is C: observational human evidence, not a randomized demonstration that these drugs prevent dementia. The Korean estimates are results in a specified type 2 diabetes comparison, not a predicted risk reduction for a person without diabetes.[7] For their established uses and the broader discussion of the class, see Book Two, *mTOR, Metabolism, and Muscle*, Chapter 12, "Acarbose and SGLT2 Inhibitors."

A large English cohort asks a more basic question: how do measured cardiometabolic factors relate to dementia among people who already have type 2 diabetes? Using records from 1999–2018, investigators studied 249,958 adults and identified 22,492 dementia cases over 1,257,998 person-years. They examined eight routinely measured factors, including fasting glucose and HbA1c. The glucose and HbA1c associations varied with follow-up period; analyses covering less than five years raised concerns about nonlinearity and possible reverse causation.[8]

Reverse causation is especially important here. Changes that precede a dementia diagnosis may alter eating, weight, medical visits, and glucose measurements. A person's recorded metabolic state shortly before diagnosis may therefore reflect early disease, rather than cause the disease observed later. Longer separation between measurement and outcome can help probe that problem, though it introduces others, including changes in treatment over time. The study's value lies in describing risk patterns under real-world care, not in defining a new HbA1c target for cognition.[8]

A cohort cannot tell a clinician to pursue the lowest possible glucose reading to protect memory. Diabetes care has to account for benefits and harms in the condition being treated, including the danger of overly aggressive glucose lowering in some patients. Nor does a glucose–dementia association show that inducing diabetes remission prevents dementia. Exposure, treatment, and outcome must be distinguished. The English findings provide C-grade dementia-risk information for glucose control and diabetes care. C meaning observational human evidence, while care for diagnosed diabetes remains standard care for its established indications.[8]

Another 2026 study illustrates how quickly the comparison becomes more complicated when the outcome is a recorded cognitive disorder rather than a glucose measure. A US electronic-health-record analysis included 1,528,885 adults aged 40–69 with type 2 diabetes and matched treatment groups using propensity scores. Compared with metformin alone, metformin plus a GLP-1 receptor agonist was associated with lower recorded incidence of Alzheimer's disease, vascular dementia, and mild cognitive disorder. Metformin plus an SGLT2 inhibitor was associated with lower vascular dementia incidence, but not lower incidence of the other measured cognitive outcomes. The authors cautioned that the associations were not causal.[9]

Those differences among outcomes resist a single slogan. A vascular-dementia association might be compatible with benefits arising partly through cardiovascular pathways. It might also reflect whom clinicians selected for combination treatment, how often patients were seen, or which diagnoses were recorded. Propensity-score matching balances measured characteristics included in the model; it cannot balance a missing history of disease severity or a reason for prescribing that the records failed to capture. The study itself noted that findings for insulin monotherapy might reflect confounding by diabetes severity and other factors.[9]

Comparison across classes is useful precisely because the drugs are not identical. If a study finds an association for one cognitive outcome but not another, it invites more specific hypotheses than "all diabetes drugs protect the brain." But multiple comparisons also create more chances for selective attention. One might quote the most favorable association, ignore the null outcomes, and describe a ranking the study was not designed to establish. No amount of record linkage converts a treatment pattern chosen by patients and clinicians into random assignment.

The GLP-1 findings belong to a further question: whether metabolic drugs can treat symptomatic Alzheimer's disease, prevent it before symptoms, or neither. Two phase 3 trials of oral semaglutide in 3,808 people with early symptomatic Alzheimer's disease did not slow decline on their primary clinical measure at 104 weeks. That treatment result does not itself answer the prevention question in people without symptoms.[10] Chapter 6, "The GLP-1 Bet," takes up those distinct treatment and prevention tests rather than borrowing the observational comparison here as their answer.

Across these cohorts, the same metaphor meets several kinds of resistance. People with diabetes differ in disease duration and severity; drugs are selected for reasons; dementia has vascular and other forms; and a glucose reading can change during the years before diagnosis. Better methods can reduce some biases. None makes "metabolic drug associated with less dementia" equivalent to "metabolic drug prevents dementia."

Care Before Repurposing

The community's impatience is understandable. Dementia can develop after a long period in which a person feels well, and a study reporting lower risk among users of an already familiar drug is hard to read without imagining missed time. The July forum argument carried that pressure: some members wanted action before definitive evidence arrived; others worried that the evidence being offered addressed a different population or concealed a tradeoff.

The choice is often presented falsely as care *or* research-minded skepticism. Established diabetes deserves care regardless of whether any one drug eventually proves useful for dementia prevention. Treating glucose-related disease, cardiovascular risk, and complications under existing indications does not require relabeling Alzheimer's as diabetes. Conversely, taking that care seriously does not license prescribing a drug to

someone without its indication on the assumption that a dementia association will transfer to them.

The chapter's four grades mark the boundaries. Glucose control and diabetes care receive C for dementia risk: observational associations inform risk, while standard care rests on established indications, not a newly proven cognitive target. Metformin for non-diabetic prevention has a C headline, with a B-null finding for overall cognition in DPPOS alongside its limited later-dementia signal. SGLT2 inhibitors receive C for dementia associations, not a prevention claim from randomized trials. Intranasal insulin receives B-null on the tested SNIFF endpoints in people with mild cognitive impairment or mild Alzheimer's dementia.[2,3,4,7,8]

Those grades are not scores for how interesting the biology is. They attach to claims about outcomes and populations. Metformin can have an intriguing dementia comparison without having demonstrated cognitive protection for all non-diabetic adults. SNIFF can fail on its clinical endpoints without disproving every possible role of insulin signaling in Alzheimer's. SGLT2 cohorts can be large and still leave treatment selection unresolved. The metaphor becomes more useful when it helps keep those distinctions visible.

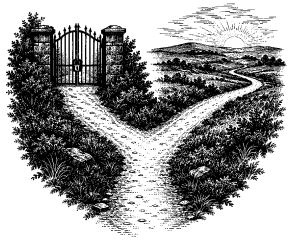
It also changes the meaning of *early*. Starting a drug before dementia is not the same as testing prevention. A prevention claim needs an appropriate population, a defined comparison, enough time, and an outcome that answers the question. A late-life analysis of survivors from an old randomized study has unusual strengths and unusual limits. A health-record cohort can observe many dementia diagnoses but cannot fully reconstruct why each person received a particular treatment. A trial in symptomatic disease can test treatment well while leaving presymptomatic prevention open.

That difference creates an uncomfortable interval between biological suspicion and clinical proof. Waiting for a long prevention study can feel passive; acting on a suggestive association can feel prudent. Yet the cost of a wrong inference is not confined to a drug's immediate adverse effects. It can include treating an uncertain benefit as established, overlooking a tradeoff with other health measures, or interpreting ordinary changes in memory as proof that an experiment worked. The forum's disagreement reflects that genuine tension, not a failure to appreciate the stakes.

For readers drawn to "type 3 diabetes," the strongest conclusion is therefore less sweeping than the name. Metabolism belongs in the

investigation of brain health. Diabetes is relevant to dementia risk. Certain drugs have associations worth testing, and one old randomization has produced a notable but qualified late-life signal. Yet the hoped-for bridge, from plausible brain mechanism to a preventive prescription for a person without diabetes, has not been built by the evidence in this chapter. The forum saw the bridge before it existed. Its best argument was not that it had already crossed, but that researchers had good reason to find out where it might lead.

Chapter 6: The GLP-1 Bet



On December 26, 2025, RapAdmin opened a forum topic whose title called the GLP-1 brain-health case Novo's "Hail Mary." The post began with a post-mortem of evoke and evoke+, two large Alzheimer's trials, and described their result plainly: oral semaglutide "failed to slow cognitive decline in early Alzheimer's disease."[1] The phrase caught a reversal in progress. A drug class that had looked unusually well placed to connect metabolic health with brain health had faced a direct clinical test, and missed.

The post did not treat the result as the end of scientific interest. It turned toward a possible metabolic mechanism that might keep the class relevant to neurodegeneration.[1] That response is understandable, but the order matters. A mechanism proposed after a failed trial cannot make the trial positive. It can suggest a different experiment, in a different population, with a different endpoint. Whether that next experiment succeeds remains unknown.

The distinction is particularly difficult here because GLP-1 drugs already have clinical uses outside Alzheimer's disease, while dementia develops over years and can be studied at several stages. As of October 2026, no GLP-1 drug is approved in the United States to prevent or treat Alzheimer's disease or dementia.[2] The question in this chapter is not whether a medicine can matter for metabolic health. It is whether evidence from one part of the body, or one stage of brain disease, supports a claim about another.

Why the Bet Looked Good

The attraction of the GLP-1 idea was not a single laboratory result. Type 2 diabetes and dementia frequently meet in the same discussion of later-life health, and drugs used in diabetes offer researchers a way to ask whether changing metabolic disease might also change brain outcomes. That makes a comparative cohort useful for generating questions. It does not make the people receiving different prescriptions interchangeable.

Consider the ordinary difficulty behind such a comparison. A person starting a GLP-1 receptor agonist may differ from someone starting another diabetes drug in weight, prior treatment, access to care, other illnesses, or what the prescribing clinician hopes to accomplish. Researchers can measure and adjust for many differences, but not every reason a treatment was chosen appears reliably in a health record. Dementia diagnosis itself depends on observation and access to assessment. These are reasons to read an association as an association, even when it is large or repeated.

There is a biological appeal, too. A medicine that produces visible effects outside the brain invites questions about inflammation, glucose handling, and processes that might operate inside it. But biological plausibility can be cheap: many interventions touch pathways implicated in Alzheimer's disease. The expensive test is whether those changes improve a clinical outcome for people who have the disease, or prevent one for people who do not. A proposed mechanism helps specify that test; it cannot substitute for it.

Earlier clinical work offered a mixed warning rather than a clean endorsement. In ELAD, a study of liraglutide, the primary cerebral-glucose-metabolism endpoint was missed; reported cognitive and brain-volume findings were secondary or exploratory.[3] Such findings may justify further investigation, but they should not be retold as success on the outcome the trial was built to test. It is precisely when the story sounds most coherent, metabolic drug, metabolic brain hypothesis, suggestive brain measurements, that the distinction between a primary result and an interesting secondary result earns its keep.

Observational comparisons in diabetes cohorts added to the interest in this drug class. They address people with type 2 diabetes receiving care, not symptom-free adults randomly assigned a medicine for dementia prevention. Prescribing patterns, follow-up, and the reasons one drug is selected over another can all shape what appears in a dementia-risk

estimate. Even a well-conducted cohort can be informative without answering whether a GLP-1 drug prevents Alzheimer's disease.

For how GLP-1 drugs work and how compounded versions are made, see *The Metabolic Frontier*, Chapters 3 and 16.

That cross-reference matters because the brain-health claim is often drawn from drugs with established effects in other domains. Approved use, however, is a statement about a particular indication supported by a particular body of evidence. A person might receive a medicine for an approved metabolic indication and later appear in a dementia study. The subsequent association does not turn dementia prevention into an approved indication, nor does it tell us that a person without that metabolic indication would obtain the same result.

Book Four, *The Metabolic Frontier*, Chapter 6 covers semaglutide's approved uses and clinical evidence.

The attraction of repurposing is easy to see from a research perspective. If a medicine is already prescribed to many people, investigators may be able to study longer-term outcomes in existing records while testing a clearer hypothesis in a dedicated trial. Those two approaches are complementary only if their questions stay separate. A diabetes cohort may help identify a signal worth testing; a trial in early symptomatic Alzheimer's disease tests whether treatment changes progression after symptoms have begun. Neither design automatically stands in for a prevention trial among adults who have no dementia.

That separation became more than a methodological nicety when evoke and evoke+ reported. Before their results, an optimistic account could fit the cohort findings, the metabolic hypothesis, and the exploratory brain findings into one continuous story. Afterward, anyone keeping that story intact had to account for a conspicuous missing piece: a clinical benefit in the large, dedicated trials.

The evoke Verdict

Evoke and evoke+ were multicentre, double-blind, randomised, placebo-controlled phase 3 trials. Together they enrolled 3,808 people with amyloid-confirmed early symptomatic Alzheimer's disease, mild cognitive impairment or mild dementia due to Alzheimer's, and followed participants for up to 156 weeks.[4,5] The studies tested oral semaglutide.[4]

Their primary outcome was change in the Clinical Dementia Rating–Sum of Boxes, or CDR-SB, at week 104.[4] CDR-SB captures changes in cognition and everyday function across domains assessed with the participant and an informant. In each trial, semaglutide failed to significantly improve the primary outcome compared with placebo. The authors concluded that it did not slow clinical progression in the population tested.[4]

This was not a small study stranded between an intriguing signal and inadequate statistical power. There were two phase 3 trials with thousands of participants and a prespecified clinical endpoint.[4] An Alzforum account of the results presented in December 2025 described the semaglutide and placebo CDR-SB curves as lying exactly on top of each other.[5] The published report that followed in March 2026 confirmed the negative clinical conclusion.[4] "Negative" here has a defined scope: no demonstrated slowing of decline on that primary measure in people with early symptomatic, amyloid-confirmed Alzheimer's disease over the period tested.[4]

A trial can fail for more than one reason. A drug might not affect the process that drives symptoms; it might affect it too weakly; or it might be tested after a useful window has closed. Those possibilities are not equivalent findings. The trial establishes the clinical result in the tested setting. Choosing among explanations for that result requires additional evidence, and a favored explanation must risk being disproved by the next study.

The Alzheimer's diagnosis in evoke also matters. Participants were not merely older adults assumed to be at risk because of diabetes or weight. They had early symptoms and confirmation of amyloid pathology.[4] This gave the trials a defined disease population, but it did not make them prevention trials. The outcome was whether treatment slowed progression once symptomatic Alzheimer's disease was present, not whether it stopped dementia from appearing years earlier.

Nor should "early" be stretched until it means "before disease." Mild cognitive impairment due to Alzheimer's is early relative to more advanced dementia, yet it is already a symptomatic clinical state. If a proposed metabolic intervention works only before substantial pathology or symptoms develop, evoke would not directly test that claim. At the same time, that narrower possibility does not erase the failed treatment claim. It becomes a new claim with its own population, endpoint, and burden of proof.

The evidence grade for GLP-1 drugs is therefore B-null for the tested early-Alzheimer treatment claim: controlled human evidence found no effect on the clinical endpoint in the population tested.[4] For prevention, the grade is Insufficient: the available evidence does not establish that these drugs prevent dementia in adults without it. “Insufficient” is not a discreet way of saying that prevention probably works. It says that the question has not been answered by evidence fitted to it.

There is an emotional asymmetry in these judgments. A hopeful observational finding can sound like a preview of a future success. A large negative trial can then sound strangely limited when researchers say it applies only to the tested population. Both reactions need restraint. The trial deserves more weight than a mechanism or a cohort association on the treatment question; its limits deserve respect on the prevention question. Refusing to call it a prevention trial is not an attempt to soften the clinical miss.

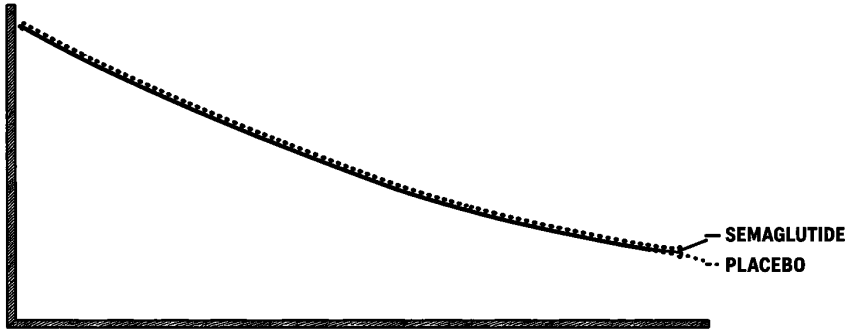


Figure 7. A schematic, not plotted data. In evoke and evoke+ (3,808 people with early symptomatic Alzheimer's disease), decline on the CDR-SB was indistinguishable between oral semaglutide and placebo at 104 weeks, and both trials were stopped (Cummings et al., Lancet, 2026).

A useful way to picture the result is as a boundary rather than a verdict on every possible use of the class. On one side sit people who already have early symptomatic Alzheimer’s disease, the clinical outcome measured at

104 weeks, and a clear failure to slow decline.[4] On the other sit people without dementia, possible changes in pathology before symptoms, and studies that still need to report results.[6,7] The boundary is not a loophole. It is a specification of what was actually tested.

Biomarkers After a Clinical Miss

The brain and blood measurements from evoke illustrate why this boundary can be hard to hold. The trials produced changes in some measured quantities even though the clinical outcome was null. An Alzforum review of the presented results reported cerebrospinal-fluid biomarker shifts of 10 percent or less, a plasma GFAP rise of about 4 percent, an approximately 30 percent fall in high-sensitivity C-reactive protein, and 5.8 percent weight loss.[5] Such changes show that something measurable happened. They do not show that symptomatic Alzheimer's disease progressed more slowly.

Not all measurements have the same relationship to the claim. Weight change and a blood inflammatory marker may register effects outside the brain. A cerebrospinal-fluid shift brings an observation closer to Alzheimer's biology, but closeness is not validation. To serve as a substitute for clinical benefit, a marker would need convincing evidence that changing it in this way predicts an outcome patients experience. When the clinical comparison has already shown no benefit, the measured shifts belong beneath it in the evidence hierarchy.

Plasma GFAP is a particularly awkward detail for a simple success story: the reported direction was upward, not uniformly toward an intuitive picture of improvement.[5] That does not establish harm by itself. It does warn against picking out only the markers whose direction suits a favored explanation. A collection of endpoints can almost always supply a promising-looking fragment if each result is allowed to speak more loudly than the prespecified clinical outcome.

Relative changes pose another trap. A roughly 30 percent fall in an inflammatory marker sounds substantial, but it is not a 30 percent reduction in cognitive decline or dementia risk.[5] Those are different outcomes with different units. Even a measured change that looks impressive beside a small cerebrospinal-fluid shift cannot be converted into a clinical effect by comparison alone. The question is not which percentage looks largest; it is whether the measure predicts something meaningful in this setting.

The same caution applies to a proposed difference between peripheral and central effects. One account of evoke's biomarker pattern is that semaglutide had evident peripheral effects without a corresponding clinical benefit in these patients.[5] It remains possible to ask whether another intervention, another stage of disease, or a more direct measure of brain pathology would tell a different story. But that is a research question formed in response to a miss. It is not a positive reading of the trials that have finished.

A biomarker can still be useful after a failed clinical trial. It may help investigators ask whether the medicine reached a proposed target, whether the target changed, or whether the original hypothesis was too simple. A small shift might suggest weak engagement, a mistimed intervention, or a marker only loosely tied to disease progression. Each interpretation calls for a discriminating experiment. Without one, competing explanations can accumulate indefinitely around the same null result.

This is also where the earlier liraglutide experience offers perspective. ELAD missed its primary cerebral-glucose-metabolism endpoint, while its cognitive and brain-volume findings were secondary or exploratory.[3] Evoke and evoke+ then missed a primary clinical outcome with semaglutide in a much larger early symptomatic Alzheimer's population.[3,4] The studies are not identical and should not be collapsed into a single estimate. Yet neither supports the claim that a positive exploratory measure outweighs the primary result.

Another metabolic idea illustrates how easily a plausible brain hypothesis can outrun its trial. In SNIFF, 289 adults with mild cognitive impairment or mild Alzheimer's dementia were randomised to intranasal insulin or placebo for 12 months. The first device proved unreliable; in the primary, second-device population of 240, change on the ADAS-Cog-12 did not differ, nor did other clinical or cerebrospinal-fluid outcomes.[8] Intranasal insulin is not a GLP-1 drug. Its place here is as a reminder that metabolic reasoning does not, by itself, establish cognitive benefit.

Book Four, *The Metabolic Frontier*, Chapter 10 covers side effects, warnings, and red flags.

That subject cannot be removed from a proposed preventive use. In established disease, an intervention's possible benefit is weighed against its burdens for people who have a defined condition. In prevention, many participants may never develop the outcome of interest, while any treatment burden occurs in the present. The longer and broader the

proposed use, the less satisfactory it is to point to a laboratory signal and leave the clinical benefit unspecified. No clinician-facing decision follows from this chapter's grade.

There is another seductive argument: perhaps a drug need not alter amyloid or tau dramatically if it improves general metabolic health and thereby reduces vulnerability. That could be a coherent prevention hypothesis. It does not explain why semaglutide should be called an effective treatment for early symptomatic Alzheimer's after two negative trials.[4] It also does not show that any eventual reduction in dementia incidence would be independent of better care for a metabolic condition. Those distinctions matter for interpreting a future positive result, not just a negative one.

The Prevention Question Remains Open

The most direct check on an easy observational narrative came from a UK primary-care study published in December 2025. Its investigators emulated a target trial among new users of GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors who were at least 60 years old and had type 2 diabetes. In the weighted GLP-1 receptor agonist versus DPP-4 inhibitor comparison, there were 13,965 people per group, with a mean age of 66.9 years.[9]

For treatment initiation, the intention-to-treat analysis did not find a lower risk of all-cause dementia with GLP-1 receptor agonists than with DPP-4 inhibitors: the hazard ratio was 0.95, with a 95 percent confidence interval from 0.87 to 1.04. The Alzheimer's disease estimate was similarly null, at 0.99, with a 95 percent confidence interval from 0.87 to 1.13.[9] These numbers are worth stating because "comparative dementia associations in diabetes" can sound more settled than the comparison actually was. The study did not reproduce a straightforward preventive advantage for starting a GLP-1 drug over that active comparator.

A hazard ratio of 0.95 is a relative estimate, not a finding that five out of every hundred people avoided dementia.[9] An absolute difference would depend on how many people developed dementia in each group over a specified period; that quantity cannot be read off the hazard ratio alone. Nor does a confidence interval spanning 1 prove the two treatments have identical effects. It indicates that this comparison did not establish a lower risk at the stated confidence level.

An as-treated analysis did find lower dementia risk during continuous GLP-1 receptor agonist use, and the authors cautioned that confounding could affect that estimate.[9] Continuous users may differ from people who stop or change treatment in ways tied to health, tolerability, adherence, or the course of diabetes. Restricting attention to time on treatment can therefore select a different kind of patient as well as a different duration of exposure. The finding is a reason to investigate persistence and its consequences, not proof that sustained use causes dementia prevention.

A target-trial emulation deserves more respect than a casual comparison of everyone ever prescribed one drug with everyone prescribed another. By defining new users and an active comparator, investigators try to make the question resemble a decision that could have been randomised. But an emulation remains observational. Its validity depends on measured covariates, recorded outcomes, analytic choices, and assumptions about what would have happened had treatment assignments differed. Here it also concerns older adults with type 2 diabetes, not all adults contemplating dementia prevention.[9]

The comparator deserves attention. "No lower risk versus DPP-4 inhibitors" does not mean "no possible effect under any comparison," because an active comparator may have its own relationship to later health. Conversely, finding a lower risk against a different comparator would not automatically establish a preventive effect. The question must specify what is being compared, for whom, and over what span of follow-up. This is why mixed diabetes-cohort associations should neither be promoted into a prevention trial nor dismissed as if they contained no information.

A separate GLP-1 prevention trial can ask a more pointed question, but even then its endpoint determines what can be concluded. ISAP is a double-blind, placebo-controlled study of semaglutide in amyloid-positive adults without dementia. Its final enrollment was 58, and its primary endpoint is annualised change in cortical tau measured by tau PET over 52 weeks; secondary measures include neuroinflammation and cognition. The registry update dated May 26, 2026, described it as ongoing and no longer recruiting, with completion expected in August 2027.[6]

ISAP is therefore not a delayed positive result from evoke. It starts earlier in the clinical course and chiefly measures a change in tau PET, not dementia incidence.[4,6] If its primary endpoint changes, investigators will still have to establish what that means for later cognition and daily function. If it does not, that result will constrain a more specific hypothesis

about this drug, population, and measure. With 58 participants, it cannot settle every preventive claim that might be attached to the drug class.[6]

PROTECT-Cog asks another question again. Announced by the Alzheimer's Association in July 2026, it is planned as a global study that combines a multidomain lifestyle intervention with assessment of a metabolism-targeting drug such as a GLP-1 agonist. The announcement describes intensive-coaching and lower-contact structured lifestyle comparisons, three years of follow-up, and cognitive and health evaluations every six months; it reports no trial outcomes.[7] It should not be described as evidence that a named GLP-1 drug has already improved cognition.

A combination study may reflect a sensible concern that later-life cognitive health is shaped by more than one process. It also creates an interpretation problem: when programs differ in contact, behavior change, and medication exposure, the design must be read carefully to know which effect a comparison can isolate. That problem is not a reason to disregard the study. It is a reason to wait for its actual design, enrollment, prespecified analyses, and results rather than using its announcement as an explanation for evoke's miss.

The forum's attention did not stay within human dementia studies. On September 2, 2026, John_Hemming opened a thread about a paper on late-life semaglutide treatment and lifespan in female mice.[10] Other members immediately disputed how much confidence to place in the result. RapAdmin shared a criticism that the control mice were short-lived relative to a historical benchmark, while another shared a reminder to "always watch the lifespan of control mice."[11,12] It was a recognizable forum exchange: interest in a striking finding met by scrutiny of the animals against which it was judged.

That thread belongs explicitly in the animal lane. A lifespan result in female mice does not measure dementia prevention in humans, and a debate about control-mouse survival does not resolve the negative human Alzheimer's trials. The result may be relevant to future aging research, but translating it into a claim about a person's brain would require several additional links: reproducibility, evidence on the relevant pathology, and ultimately clinical outcomes. None can be supplied by enthusiasm for the mouse result.

Book Four, *The Metabolic Frontier*, Chapter 22 covers the mind after food noise.

The forum post that opened this chapter shows why the GLP-1 question is unlikely to disappear after evoke. A real clinical failure can coexist with unanswered questions about earlier intervention and different outcomes.[1,4] The danger is to turn that coexistence into an unfalsifiable bet: when a symptomatic trial fails, the drug must work before symptoms; if a biomarker barely moves, perhaps the benefit lies in another pathway; if an observational comparison is null, perhaps only continuous users count. Each possibility can be stated as a hypothesis. None earns the status of a finding merely by preserving hope.

There is a better, narrower account. For early symptomatic, amyloid-confirmed Alzheimer's disease, two phase 3 semaglutide trials did not slow decline on their primary clinical endpoint.[4] In an older type 2 diabetes cohort, a carefully designed observational comparison found no lower dementia risk for GLP-1 receptor agonist initiation versus DPP-4 inhibitor initiation in its intention-to-treat analysis, although a more confounding-sensitive as-treated analysis differed.[9] Studies aimed at earlier pathology and broader cognitive-risk strategies are pending, not hidden successes.[6,7] That leaves prevention open as a question while closing the claim that evoke demonstrated treatment benefit.

Status as of October 2026

As of October 10, 2026, evoke and evoke+ remain negative for slowing clinical decline in the early symptomatic Alzheimer's population tested; they did not test prevention in people without dementia. No GLP-1 drug is approved in the United States to prevent or treat Alzheimer's disease or dementia.[2,4]

As of October 10, 2026, ISAP has no reported outcome in the cited registry update, and the PROTECT-Cog announcement reports no trial results. The May 2026 ISAP registry entry lists it as no longer recruiting with expected completion in August 2027; enrollment and readout dates for both studies should be verified against current registries before relying on them.[6,7]

Chapter 7: The Broken Plumbing



The forum's late-May 2026 digest of a University College London neurovascular review told a brain story through the condition of its vessels. The review, published the previous August, brought together research on declining cerebral blood flow, the cells that regulate it, and failures of the blood–brain barrier that can precede or interact with amyloid and tau pathology. The forum's version was more forceful: perhaps the damage begins in the blood supply, while plaques and tangles are what investigators find later. The review supported a vascular contribution and a possible feedback loop, not a verdict that vessels are the single original cause of Alzheimer's disease.

That distinction matters because "the plumbing" sounds repairable. A narrowed pipe can be opened; high pressure can be lowered. The brain's circulation is less simple. Its smallest vessels must deliver fuel to working neurons while maintaining a selective barrier, responding to local demand, and helping remove waste. A blood-pressure reading at the arm tells us something important about the system but cannot report every capillary stall or every point of barrier leakage. Nor does a plausible account of those failures establish that a particular drug will prevent dementia.

As of October 2026, two results have sharpened this chapter since the July account. One blood-pressure program reduced diagnosed dementia in a large randomized study of people with uncontrolled hypertension. A statin trial in older adults, by contrast, reduced major cardiovascular events without improving a broader outcome that included dementia. These are not opposing answers to whether vessels matter. They are a reminder that improving one vascular outcome does not automatically improve every

brain outcome, and that the precise intervention, population, and endpoint cannot be left out of the story.[1,2]

The Vascular Frame

"Blood flow" can sound like one number controlled by the diameter of one pipe. In the brain, it is an agreement among cells. Endothelial cells line capillaries and help form the blood–brain barrier. Pericytes surround those tiny vessels; astrocytes link vascular behavior to neural activity; neurons signal where energy is needed. Upstream arterioles adjust resistance, while blood cells squeeze through passages scarcely wider than themselves. When an active region needs more oxygen and glucose, this assembly must respond locally. A person can have an acceptable cuff reading and still have trouble within that assembly.

Several kinds of trouble may coexist. Arterial stiffness can alter the pressure waves reaching delicate vessels. Endothelial dysfunction and inflammation can interfere with vessel responses. Capillary stalls can interrupt delivery on a microscopic scale, while a weakened barrier may let substances cross where they ordinarily would not. Reduced flow may impede energy-dependent upkeep; vascular changes may also affect routes involved in clearing amyloid. Amyloid, in turn, can accumulate in vessel walls. The resulting loop makes a clean choice between a "vascular disease" and a "protein disease" less satisfying than either slogan suggests.

A loop also complicates the question of what came first. A vessel abnormality seen beside damaged tissue might have contributed to the injury, resulted from it, or done both at different stages. Even a measurement taken before a dementia diagnosis does not necessarily identify the first event in a disease that develops over years. The vascular account gains credibility when it predicts outcomes in people, but it should not be made into a single origin story before interventions that follow from it have been tested.

It also explains why an intervention can be worth studying without a complete account of disease origins. If high pressure damages small vessels, controlling it might reduce downstream injury even when amyloid is already present. But if pressure falls too far for a person whose circulation has adapted to longstanding hypertension, perfusion may suffer. Dizziness, falls, and other adverse effects are not objections to vascular prevention in principle; they are part of evaluating any particular

approach. The aim of research is not to declare the lowest conceivable reading a brain-protection target.

The July forum discussion displayed both sides of this attraction. Members connected the neurovascular review to insulin resistance, exercise, sleep apnea, and antihypertensive drugs, asking whether several stresses might converge on the brain's fuel supply. They also moved quickly from a systems explanation to comparisons among individual medicines. That move is understandable. If vessels are involved, why not find the best vessel drug? Yet evidence for a mechanism does not establish a dementia outcome.

One member's prolonged examination of MRI-visible perivascular spaces gave the distinction a human scale. These spaces are small channels around vessels, of interest to researchers studying fluid movement and small-vessel disease. Papers can appear to disagree about whether "more spaces" are worse because their measurements are not interchangeable: a count of visible spaces is not an average diameter, and neither number is a personal diagnosis. The July account followed a member as he corrected his own shorthand after reading a large imaging study more carefully. Another member responded less to the imaging analysis than to the strain of living inside it. The exchange belonged in the vascular story because it showed what a candidate marker can become when a worried person tries to make it speak with more certainty than it has.

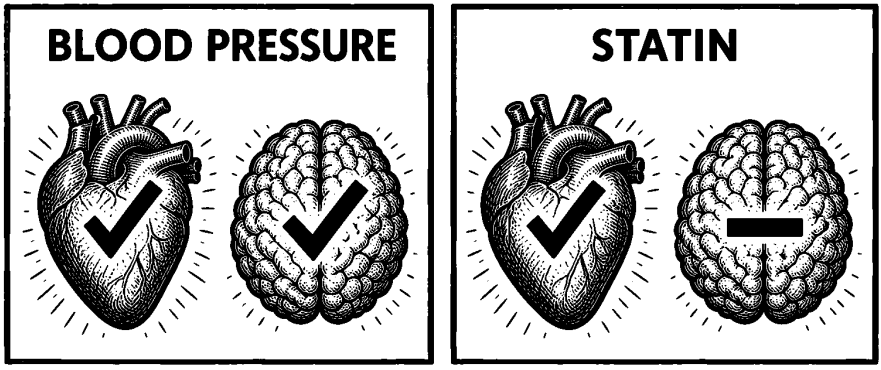


Figure 8. Heart and brain can part company. CRHCP (33,995 adults with high blood pressure in rural China) found that intensive blood-pressure control reduced all-cause dementia by about 15 percent. STAREE (9,971 adults aged 70 and older, median 5.9 years) found that atorvastatin cut major cardiovascular events by 30 percent but did not improve the composite of death, dementia or persistent disability (hazard ratio 0.94, not significant).

The figure belongs here, between the biological account and the trials, because arrows connecting vessels, inflammation, metabolism, amyloid, and cognition are not themselves evidence that pulling one arrow changes the final outcome. Randomization asks a narrower, harder question. Assign a defined intervention to a defined population, follow both groups, and count a specified result. Even then, an answer may apply most securely to the people and care setting actually studied.

For broader vascular prevention context, see Book One, *The Longevity Operating System*, Chapter 15, “Dementia Prevention Without Magical Thinking.”

The Pressure Trials

The China Rural Hypertension Control Program, or CRHCP, offers the strongest prevention claim in this book. Its grade is B: a controlled human signal with limits, rather than a promise for every patient or a replicated result in every setting. In 326 rural Chinese villages, investigators enrolled 33,995 adults aged 40 or older with uncontrolled hypertension. Villages were assigned either a village-doctor-led intensive blood-pressure program or usual care; dementia outcomes were assessed with blinded endpoints, although the intervention itself was open-label. At 48 months, the intensive group had a lower risk of all-cause dementia: risk ratio 0.85, with a 95 percent confidence interval of 0.76 to 0.95. Serious adverse events were also fewer in that group.[1]

The ratio is worth translating carefully. A risk ratio of 0.85 represents a 15 percent *relative* reduction compared with the usual-care group at that follow-up; it does not mean that 15 percent of everyone enrolled avoided dementia.[1] The absolute difference depends on how often dementia occurred in the comparison group over the period studied. That distinction becomes especially important when a headline travels from a population with uncontrolled hypertension to one with a different starting risk. The same relative effect, if it held, would not necessarily imply the same number of cases prevented.

The setting is part of the finding, not background decoration. This was a delivery program for people whose hypertension was uncontrolled, carried out through village doctors across a large rural population. It tested what happened when an organized system improved pressure control compared with usual care in that setting. It did not isolate one drug, compare telmisartan with another ARB, or ask whether someone whose pressure is already controlled should pursue a lower number for brain protection. Its published four-year outcome is unusually direct because it counted dementia rather than relying only on a scan, laboratory marker, or short cognitive test.[1]

There is a design tradeoff in that practicality. Assigning whole villages allowed the investigators to study a care program as it could operate across communities, rather than treating each person's prescription as the entire intervention.[1] But an open-label program also makes it harder to know which features of changed care produced the benefit. Blinded assessment of endpoints helps protect the dementia comparison from knowledge of assignment; it does not turn the program into a blinded test of one

mechanism.[1] A reader looking for the uniquely protective medicine will not find it in this trial.

In August 2026, a European Society of Cardiology conference report described seven-year follow-up from the same program. Dementia was reported in 8.85 percent of the intensive-intervention group and 10.55 percent of the usual-care group, with an adjusted risk ratio of 0.85. That is an absolute difference of 1.70 percentage points over the reported seven years, alongside a relative reduction of about 15 percent.[3] The longer observation supports persistence of the original signal, but it is not a second independent trial. As of October 2026, the seven-year result had been reported at a conference; the peer-reviewed publication covered 48 months. That distinction matters when the two time points are mentioned together.[1,3]

The distinction between longer follow-up and replication matters. Seeing an effect persist in the same study addresses one concern: that the early difference might disappear with more time. It does not show that a different health system would achieve the same result or that another trial team would measure precisely the same effect. Nor should the seven-year percentages be treated as a forecast for an individual reader. They describe the groups followed in this program.[3]

SPRINT MIND provides the necessary contrast. It enrolled 9,361 adults with hypertension; the median intervention period was 3.34 years and median follow-up was 5.11 years. Intensive control reduced mild cognitive impairment, or MCI, with a hazard ratio of 0.81, and reduced the combined MCI-or-dementia outcome, with a hazard ratio of 0.85. Probable dementia was numerically lower, 7.2 versus 8.6 cases per 1,000 person-years, but the hazard ratio of 0.83 had a 95 percent confidence interval from 0.67 to 1.04. That dementia result was not statistically significant. The trial stopped early because of cardiovascular benefit, limiting the time available to observe an outcome that may take years to emerge.[4]

Those rates put the dementia comparison on an absolute scale: the difference was 1.4 cases per 1,000 person-years of observation, even though the estimated relative difference was larger.[4] The confidence interval included a result consistent with no reduction in probable dementia. That does not make the MCI finding disappear. It does mean that a combined endpoint, which can register more events, must not be substituted for its dementia component when describing what the trial established.[4] A change

in cognitive impairment short of dementia matters, but it is not the same result as fewer diagnosed dementia cases.

Neither trial needs to be forced into the other's wording. Saying SPRINT MIND "proved dementia prevention" would erase its nonsignificant probable-dementia result. Saying pressure control has only a surrogate brain signal would erase CRHCP's dementia outcome. Together, they support a stronger case for treating uncontrolled hypertension than this book can make for most proposed prevention interventions, while preserving uncertainty about how results transfer across populations and care systems. The B grade belongs to blood-pressure control as a prevention claim; it does not attach equally to every target, every antihypertensive drug, or every person who might take one.[1,4]

The pressure trials also help sort two explanations that forum threads often run together. Better control could protect the brain principally by reducing vessel injury. Alternatively, some medicines might have additional effects unrelated to the pressure they achieve. Herm raised the second possibility in an August 2026 reply: "It's possible that the medications used to control blood pressure may have other target effects related to brain ageing."[5] It is a legitimate research question, but CRHCP did not settle it. To claim that one class has a special cognitive advantage would require evidence able to separate drug identity from achieved pressure, reasons for prescribing, adherence, and other differences among patients.

That is why the result does not turn blood pressure into a contest for the most aggressively lowered reading. The observed benefit arose in adults with uncontrolled hypertension receiving a program of care.[1] Someone already treated may have a different balance of possible gain and harm. Someone prone to fainting may experience a change that a trial average conceals. The population-level finding is meaningful without being converted into a universal instruction.

A Statin Split Verdict

If CRHCP shows why a vascular risk factor deserves serious attention, STAREE shows why cardiovascular success cannot be silently relabeled dementia prevention. Published in August 2026, the trial randomized 9,971 community-dwelling adults aged 70 or older who did not have cardiovascular disease, diabetes, or dementia. One group received atorvastatin, the other placebo; median follow-up was 5.9 years. Major cardiovascular events were lower in the statin group, with a hazard ratio of 0.70 and a 95 percent confidence interval of 0.61 to 0.82. Yet the trial's composite outcome of death, dementia, or persistent physical disability was not significantly improved: hazard ratio 0.94, confidence interval 0.84 to 1.05.[2]

This is a split verdict, not a failed drug. The cardiovascular benefit is substantial within the trial's population and endpoint. The null composite means that a benefit on major cardiovascular events did not translate into a statistically demonstrated benefit on that broader measure during the observed period. A composite is also not the same thing as a dedicated standalone dementia result: changes in its components can differ, and the published trial report does not establish that atorvastatin prevented dementia on its own. The American College of Cardiology's contemporary summary likewise distinguished fewer cardiovascular events from the lack of improvement in disability-free survival, which included dementia.[2,6]

A composite can answer a sensible question while leaving another one unsettled. Death, dementia, and persistent physical disability all matter to an older adult's independence, but they are not interchangeable biological events. A trial could reduce one component and have little effect on another; the overall estimate would reflect their combined frequency and timing. Conversely, a nonsignificant composite does not prove that every component had exactly no effect. STAREE's published composite supports restraint about a broad benefit, not a confident claim of dementia prevention on its own.[2]

For the dementia-prevention claim in healthy adults aged 70 or older, statins and LDL lowering receive B-null: controlled evidence that did not show a benefit on the endpoint tested. The grade does not mean that statins cause cognitive harm. Nor does it cancel their cardiovascular benefit or answer every question about starting treatment earlier, treating people at a different level of risk, or following them for longer. A null brain-related

outcome and a positive heart-related outcome can coexist without either being explained away.[2,6]

The hazard ratio of 0.70 for major cardiovascular events is sometimes rendered as "about 30 percent fewer." That is a relative comparison, not a statement that 30 of every 100 participants avoided an event; the reported hazard ratio alone does not give the absolute event difference needed for that claim.[2,6] The distinction protects against two opposite mistakes: dismissing a meaningful cardiovascular result because the composite was null, and borrowing the cardiovascular percentage to advertise an unproved dementia benefit.

High LDL cholesterol's place in dementia-risk models can make this result seem puzzling. The 2024 *Lancet* Commission added high LDL cholesterol to its list of modifiable dementia risk factors. A risk-factor designation identifies an association judged relevant to prevention modeling; it is not proof that lowering LDL with a medication, at any age and over any duration, will reduce diagnosed dementia. Timing may matter: vascular exposure can accumulate long before a person turns seventy. Outcomes may matter too: preventing a cardiovascular event is directly measurable within a trial even if an effect on later dementia is absent, smaller, or takes longer to detect. These possibilities do not overturn STAREE. They define questions that STAREE did not answer.

The comparison with CRHCP is tempting but should be handled carefully. The trials studied different populations and different interventions. CRHCP addressed uncontrolled hypertension through a care program beginning at age 40 and counted all-cause dementia. STAREE studied a statin in initially healthy adults aged at least 70 and reported a null composite that included dementia. One cannot infer from their different results that pressure is biologically important and cholesterol is not. One can say that the controlled dementia claim is stronger for blood-pressure control in the CRHCP setting than for starting the tested statin in the STAREE population.[1,2]

Markers Are Not Brain Levers

The vascular frame encourages measurement. If the brain depends on healthy vessels, perhaps a more precise blood marker will reveal which part of prevention has been missed. ApoB, a marker of atherogenic lipoprotein particles, and lipoprotein(a), or Lp(a), are discussed in cardiovascular risk assessment. Stroke and cardiovascular disease are relevant to brain health. Still, identifying a vascular marker is not the same as demonstrating that measuring it differently, or changing its concentration, prevents dementia.

A large UK Biobank analysis published in November 2025 illustrates the difficulty for ApoB. It examined 308,019 participants and recorded 5,445 incident dementia cases, including 2,617 classified as Alzheimer's disease and 1,212 as vascular dementia. Across 39 biomarkers and six metabolic profiles, associations differed by profile and dementia subtype. In the main Alzheimer's analysis, ApoB was not clearly associated with risk: hazard ratio 1.03, with a 95 percent confidence interval of 0.99 to 1.07. After adjustment for APOE-ε4 allele count, the reported association became inverse, with a hazard ratio of 0.92.[7]

That reversal is not an invitation to raise ApoB for the brain. It shows how an observational estimate can depend on the model, particularly where a gene strongly related to Alzheimer's risk also relates to lipid patterns. The study did not assign participants to change ApoB and observe whether dementia followed. For ApoB as a demonstrated brain lever, the grade is Insufficient: no published intervention study has shown that changing it prevents dementia. Its cardiovascular relevance is a separate claim.[7]

The subtype differences matter as well. "Dementia" combines outcomes that need not have identical relationships with a lipid marker. In this analysis, Alzheimer's disease and vascular dementia were counted separately among the recorded cases, and risk patterns varied across metabolic profiles and dementia subtypes.[7] A single headline about ApoB and "the brain" would flatten those distinctions. Yet dividing cases into smaller categories can also leave estimates less certain. More precise labels do not automatically produce a causal answer.

Lp(a) requires similar restraint. It is a cardiovascular or stroke-risk marker, but measuring it has not been shown to change dementia incidence, nor has lowering it been shown to prevent dementia. As a demonstrated dementia-prevention lever, its grade is Insufficient. It would be especially easy here to turn a marker's value in one clinical domain into an implied

treatment target for another. That transfer needs an outcome study, not a persuasive account of vascular biology.

PCSK9-targeted therapies offer a sharper test of the assumption that successful lipid intervention must be successful dementia prevention. An August 2026 meta-analysis pooled 22 randomized trials involving 64,116 participants; its search covered trials through January 2025. It found lower all-cause stroke risk with PCSK9-targeted treatment, odds ratio 0.78, and lower ischemic stroke risk, odds ratio 0.77. Dementia was not significantly associated with treatment: the odds ratio was 0.77, but its 95 percent confidence interval ran from 0.14 to 4.28. The estimate for Alzheimer-type dementia was similarly imprecise. These were dementia-event data from trials, not a dedicated, long-term program of cognitive testing.[8]

It is possible to mistake the point estimate of 0.77 for a finding of dementia protection because it lies below one, just as the stroke estimates do. The uncertainty intervals tell a different story. For dementia they are wide enough to admit markedly different effects, while the stroke intervals support a more definite reduction.[8] Pooling many participants does not guarantee a precise answer for an outcome that the underlying trials were not chiefly designed to examine. The number enrolled and the number of informative dementia events are different quantities.

The most defensible reading is reassuring on cognitive safety without claiming proven protection. A reduction in stroke is a real vascular result; the dementia estimate is too uncertain to determine a preventive effect. The wide interval also means it cannot establish the absence of every possible harm. For PCSK9 inhibitors as dementia prevention, the grade is Insufficient, with randomized event data that have not established a dementia harm signal. This is a different verdict from calling the drugs either “brain-protective” or “bad for the brain.”[8]

The contrast exposes a persistent error in prevention talk. A biomarker may predict a disease, an intervention may change that biomarker, and the intervention may improve an outcome closely related to it. None of those steps alone establishes a later dementia benefit. Some pathways converge; others diverge. Stroke reduction can matter greatly without producing a detectable dementia signal in trials assembled for different primary questions. Likewise, observational dementia associations can be altered by who was tested, who received treatment, how long they were followed, and which dementia subtype was counted.

This is where the pressure result stands apart. CRHCP did not merely show a better pressure number and ask readers to assume the brain benefited. It counted fewer dementia cases in a randomized comparison among people with uncontrolled hypertension. That does not solve every question about mechanism or individual care, but it crosses a boundary that marker studies and most drug-repurposing arguments have not crossed.[1]

The July Drug Detours

In the July account, the vascular review led forum members toward two drugs that sat well below blood-pressure control as a dementia-prevention claim: telmisartan and bumetanide. They deserve separate treatment because their proposed roles are different. Telmisartan is an angiotensin receptor blocker, or ARB, whose ordinary clinical role is blood-pressure treatment; the forum asked whether its particular pharmacology might offer cognitive advantages beyond pressure control. Bumetanide entered as a repurposing idea, not as a standard substitute for vascular care. Neither question was answered by CRHCP.

For ARBs, including telmisartan, the brain-specific prevention grade is C: observational or uncontrolled human evidence, not a randomized dementia outcome establishing a special advantage for the class or molecule. ARBs share a principal receptor target but differ in other pharmacologic properties. Telmisartan's proposed metabolic effects made it particularly attractive in forum debate. The appeal of those properties is a reason to test a hypothesis, not a reason to promote a receptor diagram into a clinical endpoint.

The July chapter followed members arguing about telmisartan against other ARBs, checking one another's claims, and reporting widely different experiences of tolerability. An observational comparison of antihypertensive users also entered the conversation. Such comparisons can be useful for generating questions, but treatment choice is not random: kidney disease, diabetes, prior side effects, prescribing habits, and adherence can differ between groups. An apparent agent-level dementia advantage might reflect some of those differences even after statistical adjustment. The clinical question is not simply whether two medicines act differently in a laboratory; it is whether a fair comparison finds meaningfully different brain outcomes at tolerable levels of blood-pressure control.

A further difficulty is separating the drug from the condition it treats. People who receive one ARB rather than another may also differ in how long their pressure has been uncontrolled, how often care is available, or why a clinician changed treatment. Even if a comparison accounts for recorded differences, an unrecorded reason for prescribing can remain. That limitation does not make every observational signal worthless. It sets a ceiling on how confidently such a signal can identify a brain-specific effect.

One July 2026 forum post makes the cost of overlooking tolerability plain. DeStrider wrote, "I tried taking Telmisartan again but again suffered the effects of low blood pressure." The member also reported having fainted on a previous occasion. This is an individual report, not a measure of how often that reaction occurs, but it is a useful counterweight to the idea that a plausible extra brain effect would make a particular drug desirable regardless of how someone feels on it.[9] The blood-pressure program's benefit cannot be assigned to telmisartan, and a proposed telmisartan advantage cannot excuse symptomatic pressure lowering.

Bumetanide presents another kind of gap between biological interest and demonstrated prevention. The July account treated its repurposing discussion as a lower-grade claim, not as a finding that it protects people without dementia. Its grade here is C, meaning that the human evidence under discussion is observational or uncontrolled and does not establish the preventive endpoint. It is not interchangeable with the B assigned to blood-pressure control. Considering a medicine for a new brain purpose also entails its established medical uses, adverse effects, and the consequences of displacing indicated care. That is why repurposing belongs as a question for a clinician and for properly designed studies, not as a prescription offered by a prevention book.

The distinction is easy to lose because the vessel story is unusually coherent. Insulin resistance, pressure, endothelial behavior, inflammation, lipid transport, and clearance can be placed on one diagram; each offers an entry point for a possible intervention. But a coherent diagram can contain several interventions whose outcome evidence differs sharply. In this chapter, blood-pressure control reaches a controlled dementia endpoint in people with uncontrolled hypertension. Statin treatment reduces major cardiovascular events in a healthy older trial population without demonstrating the tested broader outcome. ApoB and Lp(a) remain markers rather than demonstrated dementia levers. Randomized PCSK9 data show fewer strokes but leave dementia effects uncertain. Telmisartan's

proposed extra effects and bumetanide's repurposing rationale remain below the controlled dementia evidence.[1,2,7,8]

There is a warmer reading of the forum's detours than simply calling them overreach. Members noticed a serious scientific review, looked for mechanisms that might connect diseases usually kept in separate clinical compartments, and sometimes corrected their own claims in public. The same curiosity can, however, collapse the distance between "this vessel pathway matters" and "this medicine will protect my brain." Holding that distance open is the work of evidence grading. It lets a promising idea stay promising without pretending it has already passed the trial that would decide it.

The broken-plumbing metaphor survives, with a qualification. Some damage to the brain's circulation may be preventable, and the controlled blood-pressure result gives that proposition a consequential human outcome.[1] Yet the brain is not a sink, and there is no single valve whose adjustment settles its future. The strongest vascular finding points toward sustained care for an established condition, not a new molecule marketed as a shortcut around it. From here the account turns to movement: another intervention with powerful effects throughout the body, and another case in which benefits to health must be distinguished from proof of dementia prevention.

Part III: Building Reserve

Chapter 8: The Exercise Prescription Nobody Can Patent



On September 17, 2024, in a forum thread asking which agents might protect the brain, desertshores put the central problem plainly: “I need help finding scientific evidence for any drug or supplement that has any solid evidence that it is neuroprotective.”[1] The question was fair. So was the thread’s interest in testing claims rather than trusting a familiar ingredient or a plausible mechanism.

Yet exercise could almost disappear in a conversation framed around *agents*. The next day, adssx included physical exercise among practices described as proven, alongside sleep, stress management, and cognitive activity.[2] In the thread’s rhythm, it risked becoming a passing assumption while the replies searched for more exotic possibilities. Familiarity can make an intervention look settled even when the question attached to it, better performance on a cognitive test, slower decline, or fewer dementia diagnoses, has not been specified.

The discussion also showed how much can fit under the word *protection*. On September 17, Melih’s entire contribution was “first place: social bonds”.[3] That brief answer did not establish an outcome, but it resisted the assumption that the best candidate must be a substance. Exercise belongs in the same awkward category: consequential enough to examine carefully, yet easy to overlook when a conversation asks for an agent.

That omission is worth correcting without turning exercise into a miracle drug. It has randomized evidence for some cognitive outcomes, observational evidence relevant to dementia, and an unusually rich collection of proposed biological pathways. Those are different kinds of

evidence. If the forum asks a peptide to show that it changes human cognition rather than merely shifting a molecular marker, exercise deserves the same test. If it passes one test and not another, both findings belong in the account.

The Taken-for-Granted Intervention

Exercise is difficult to discuss as a single exposure. Aerobic work, resistance training, and brief high-intensity efforts ask different things of the body. A study may measure fitness, executive function, mood, blood chemistry, or a dementia diagnosis years later. Calling all of these "brain health" conceals the distance between them. A stronger score on a task requiring attention and mental flexibility is interesting; it is not a count of people who did or did not develop Alzheimer's disease.

That distinction governs this chapter's grades. Aerobic and resistance exercise receive C for dementia prevention: C means observational or uncontrolled human evidence for that headline claim, not a randomized demonstration that exercise prevents dementia. They receive B for small cognitive outcomes: B means a controlled human signal with limits. HIIT receives Insufficient for cognitive protection: the available randomized results do not support a consistent protective claim. These grades attach to specified outcomes, not to a verdict on whether physical activity is worthwhile for other reasons.

The April 2026 three-level meta-analysis offers a particularly useful point of entry. It synthesized randomized exercise trials assessing executive function in cognitively healthy adults aged 60 or older. Aerobic exercise was associated with a small improvement, with a reported standardized effect of $g = 0.130$; resistance training also showed a small improvement, $g = 0.232$.[4] Random assignment makes these results more informative about an intervention than an observation that active people tend to score better. The small effect sizes, the selected outcome, and the cognitively healthy study population also set their boundaries.

Neither g value is a percentage reduction in dementia risk. A standardized effect describes a difference relative to the variation in test scores; it does not say how many additional people remained independent, avoided a diagnosis, or noticed a change.[4] This matters when a numerical result travels beyond the paper. A decimal can look precise while the everyday meaning of the measured difference remains uncertain.

Executive function is not a decorative endpoint. It includes capacities used to hold a task in mind, resist distraction, and change course when a rule changes. But a test of those capacities may be affected by practice, effort, fatigue, or other short-term influences, and a pooled change need not describe what any one participant notices in ordinary life. A trial can detect a modest average signal without establishing that it changes the later incidence of dementia. The trials in this synthesis addressed executive-function outcomes; they did not collectively become a randomized exercise trial powered to count new dementia cases over many years.[4]

The missing trial matters because dementia prevention is a harder and slower claim. People enter later life with different education, health histories, genes, vascular risks, and levels of activity. Dementia itself has multiple causes, and a cognitive score can change without a corresponding change in disease incidence. To test the prevention claim directly, an exercise study would have to distinguish the intervention from what its comparison group does, retain participants long enough for clinical outcomes to emerge, and account for changes in health and activity along the way. The executive-function findings cannot answer that question by proxy.

Observational comparisons fill some of the gap, but not all of it. Someone who stays active may also have better access to care, fewer disabling illnesses, or greater ability to remain socially engaged. Conversely, a developing disease may reduce activity years before diagnosis, making inactivity appear to be an early cause when it is partly an early consequence. Statistical adjustments can reduce these problems; they cannot establish the same counterfactual as random assignment. That is why the prevention grade remains C even when exercise seems more credible than many purported neuroprotective agents.

Reverse causation is especially troublesome here because the behavior being studied requires physical and cognitive capacity. Someone who becomes less active may be responding to subtle changes that have not yet been recognized as symptoms. Someone who remains active may be showing the benefits of a favorable starting position as well as any effect of activity itself. The apparent contrast between them can be real without having a single, simple cause.

This is not a ranking of pleasures or virtues. An intervention can be sensible for health reasons while its dementia-specific claim remains

uncertain. It can also improve a measurable cognitive task without supplying a recognizable difference in daily life. Treating those statements as compatible is more honest than forcing exercise into either the "proven prevention" or "just a lifestyle habit" box. For general fitness guidance, see Book One, *The Longevity Operating System*, Chapter 5, "Fitness Is a Longevity Intervention."

The distinction also protects readers from an odd double standard. A novel compound may attract skepticism because its advocates show a laboratory marker instead of a clinical outcome. Exercise tends to receive the opposite treatment: its many benefits elsewhere are sometimes allowed to stand in for proof about dementia. The proper comparison is claim by claim. Does an intervention change a controlled human cognitive endpoint? Does it change a validated clinical endpoint? Does it reduce diagnoses? Are any observed differences large enough and durable enough to matter? Evidence for one answer should not silently supply another.

What Controlled Training Changes

The aerobic result in the meta-analysis is modest, but modest is not meaningless. In cognitively healthy older adults, randomized trials collectively associated aerobic exercise with a small gain on executive-function tests.[4] That is more than a speculative story about blood flow or a mouse maze. It is also less than proof that a person who becomes more active will remain free of dementia. The measured endpoint is a performance difference within the conditions of the trials, and the grade B belongs to that narrower claim.

Resistance training deserves its own reading rather than being treated as an accessory to aerobic exercise. The same 2026 synthesis found a small executive-function association for resistance interventions in cognitively healthy adults aged at least 60.[4] Its reported effect size was larger than the aerobic estimate, but comparing the two pooled numbers as though they came from a single head-to-head contest would overstate what they tell us.[4] Different trial populations, comparisons, and tests can influence pooled estimates. "Larger in this analysis" is not the same as "the superior way to prevent dementia," an outcome these studies did not establish.

The separation matters in real life because a person's capacity to take part in one form of activity does not necessarily predict capacity for another. Aerobic and resistance trials also differ in what success outside the cognitive test might mean. Better physical function can make an activity

valuable without proving a direct effect on brain disease. If a participant feels more capable of ordinary tasks, that experience has its own importance; it should not be retroactively counted as evidence of fewer future Alzheimer's diagnoses.

A useful complication is the comparison group. Exercise trials cannot assume that people assigned elsewhere simply cease moving. Some controls receive attention, health information, or another active program. A small difference against an active comparator could understate a benefit relative to inactivity; a difference against a less engaging comparison could partly reflect contact and expectation. These possibilities do not make randomization useless. They show why a pooled result needs its trial context, especially when the average cognitive change is small.

There is an absolute-versus-relative trap here, too. If two groups both improve on a test, a small difference between them does not mean the intervention group barely changed. Equally, improvement within the intervention group does not show that exercise caused it; the comparison group might have improved as well. The randomized contrast, not the most encouraging before-and-after score, carries the causal question. And even that contrast concerns the test administered, not a later clinical event.

Controlled lifestyle studies raise a related temptation. A structured program can combine exercise with changes in food, risk-factor care, social contact, or cognitive activity and show a cognitive signal. That supports the package tested, not an isolated claim about exercise. Separating the ingredients afterward is difficult: the people who engage with one component may engage with others, and the components may work together. A reader cannot take a favorable composite score, assign all the credit to movement, and then treat it as evidence for dementia prevention.

Exercise also refuses the simple identity of a pill. A drug trial can often compare a defined product with an inert-looking substitute. In training studies, participants usually know whether they are exercising, the intervention changes with their ability to participate, and the comparison may have effects of its own. Cognitive testing can be blinded even when the intervention cannot be hidden. That makes careful trial design more important, not less, and it gives a reason to resist confident claims based on any single small result.

The 2026 meta-analysis reported a significant effect in its moderate-intensity subgroup, $g = 0.254$, while its pooled high-intensity subgroup estimate was not statistically significant.[4] This is a finding about

the studies grouped under those labels, not a prescription for effort or proof that higher intensity is harmful. The people, exercise formats, comparison conditions, and executive-function tests represented in each subgroup may differ. A subgroup result can generate a question; it cannot by itself settle the best intensity for protecting an aging brain.

There is another subtlety in the word *change*. A small gain on an executive-function task may reflect a real improvement in performance while leaving open how long it lasts. A longer-lasting effect would be more persuasive for building cognitive reserve, yet durability requires follow-up rather than an appealing mechanism. The question also changes when people already have mild cognitive impairment: a finding in cognitively healthy adults cannot simply be carried into a group with symptoms. The April synthesis was explicitly about cognitively healthy people aged 60 or older.[4]

The cautious interpretation is neither "exercise does nothing" nor "exercise prevents Alzheimer's." Aerobic and resistance studies give controlled evidence of small improvements on selected cognitive tests in older adults without cognitive impairment.[4] The prevention claim remains an inference supported at a lower grade, vulnerable to confounding and to the long interval between behavior and diagnosis. The difference between those statements is where much of the chapter's practical honesty lies.

Intensity's Unfinished Case

The forum did not always leave exercise in the background. In a separate discussion opened on March 27, 2024, RapAdmin wrote, "We need high intensity exercise to maximize brain health…"[5] The post pointed toward research on motor-cortex plasticity after an exercise bout, a plausible subject of interest but not the same endpoint as memory preservation or a later dementia diagnosis.[5] The word *maximize* does heavy work. It turns a question about one measured response into a broad claim about the brain.

Other members brought lived experience to the intensity discussion. On April 6, 2025, RobTuck described subjective improvements in well-being, balance, and energy associated with short, hard efforts, while acknowledging the lack of good metrics for those impressions.[6] Such reports can tell investigators what outcomes people notice and which questions feel worth studying. They cannot determine whether intervals protect cognition better than less intense activity. Well-being and energy matter, but neither is a dementia endpoint.

The randomized literature is much smaller than the confidence of some claims. An August 2026 review found five randomized trials of high-intensity interval training, or HIIT, in healthy adults aged 60 or older. It did not find a consistent benefit for overall cognition. Some individual studies reported gains in selected areas, including working memory or hippocampal-dependent learning, but outcomes differed and active exercise comparison groups complicated interpretation.[7] Five varied trials are enough to ask better questions. They are not a secure basis for declaring one intensity necessary for cognitive protection.

The meta-analysis of executive function supplies a second check: its moderate-intensity subgroup showed a statistically significant pooled effect, whereas its high-intensity subgroup did not.[4] That does not prove moderate activity beats HIIT. "Significant here, not significant there" is not itself a head-to-head difference. It does, however, challenge the stronger assertion that cognitive benefit clearly rises with intensity. When the relevant randomized evidence is limited and inconsistent, the proper grade for HIIT as cognitive protection is Insufficient.

Intensity studies face several interpretive traps. A brief intervention might alter alertness or performance on a particular task without altering the course of disease. A comparison against another kind of exercise asks whether one format differs from another, not whether movement differs from no movement. If tests sample only a few cognitive domains, an improvement in one domain can sit beside no clear change overall. The review's combination of selected positive findings and inconsistent overall results illustrates exactly this problem.[7]

A positive result on a selected test also attracts more attention than a set of inconclusive results. That does not make the positive result false. It means the relevant question is whether a pattern holds across trials that ask comparable questions. Here, differences in outcomes and active comparators make that pattern hard to see.[7] The uncertainty cannot be repaired by choosing the most appealing finding and calling it the verdict.

Nor can laboratory measures of cortical responsiveness settle it. A response to a single exercise session may illuminate how the nervous system reacts under controlled conditions. It is several steps removed from a lasting improvement in daily cognition, and further still from prevention of dementia. The intermediate measurement can be worth studying without being promoted to the clinical outcome. The same standard would apply to an experimental drug that altered a brain signal for an afternoon.

There is a cost to treating the hardest effort as the default ideal. An intervention that looks promising in those able and willing to complete it may be poorly represented among people with substantial physical limitations or medical complexity. That is a question of who enters a trial and who remains in it, not an argument against studying intensity. It also means that any future cognitive finding would need to be read alongside adverse events, participation, and the comparator. Exercise safety remains a separate question; it does not convert an unsettled cognition claim into an intensity rule.

The forum's intensity debate is valuable when kept in its proper form: a hypothesis under active test. Participants' accounts convey motivation, bodily limits, and outcomes that matter to them. The five-trial review conveys what randomized cognitive studies have so far managed to show.[7] Neither should be asked to do the other's job. A subjective sense of sharper functioning may justify curiosity; it does not close the case. For rapamycin and exercise, see Book Two, *mTOR, Metabolism, and Muscle*, Chapter 6, "RAPA-EX."

Messages From Muscle and Liver

Why might movement affect cognition at all? One line of research asks whether working tissues send chemical signals that influence the brain or its blood vessels. Such signals are often called *exerkines*. The idea is attractive because it offers a chain from physical activity to a molecular messenger to a measurable brain effect. Yet each link requires separate evidence. Detecting a circulating substance after exercise does not show that changing it will improve a person's memory.

GPLD1 provides an unusually vivid example. In a February 2026 *Cell* study, researchers examined this liver-derived, exercise-associated factor and its vascular target, TNAP. In aged mice, increasing GPLD1 or inhibiting TNAP improved reported measures of the blood–brain barrier and memory-related outcomes. In a mouse model of Alzheimer's disease, those manipulations reduced amyloid pathology and improved measured cognitive deficits.[8] That is a striking mechanistic result. It is also a result in mice, produced through experimental manipulation, not a human trial of exercise-induced GPLD1 changes.

The vascular finding makes the story especially appealing after a chapter on the brain's "broken plumbing." It suggests a route by which a peripheral signal might matter even without a simple claim that the messenger enters

the brain and repairs neurons.[8] But a plausible route is still a route under investigation. Mouse models reproduce selected features of aging or Alzheimer's-related pathology, not the full, varied human disease. Improving a mouse memory task and blood–brain barrier measures cannot establish reduced dementia incidence in people.

The next human study made the picture less tidy. A June 2026 report measured plasma GPLD1 in 19 young adults, 526 older adults, and 38 adults with prediabetes. In the young-adult exercise group, moderate exercise over seven weeks did not change measured GPLD1; habitual activity over three months did not change it in the prediabetes group either.[9] These are not definitive tests of every kind of exercise, every person, or every time frame. They do test a simple expectation generated by the phrase "exercise-associated factor": that more activity in these human settings would produce a detectable increase.

Among the older adults, the initially striking observation ran in an awkward direction: higher average steps correlated with *lower* GPLD1 before adjustment. That association was no longer present after accounting for diabetes status. The investigators said human links between GPLD1 and cognition needed further study.[9] The disappearance after adjustment is not proof that diabetes explains everything. It is a reminder that a blood measure can track other features of health and that an apparent activity relationship can be sensitive to how those features are handled.

The two human exercise groups were also small relative to the older-adult cohort in which the steps association was examined.[9] That limits what can be concluded from an unchanged blood measure. A negative result in those settings does not erase the mouse mechanism. It does, however, block the easy story in which exercise reliably raises plasma GPLD1 in people and that rise can be assumed to protect their brains.

Most importantly, this human study did not show that changing GPLD1 improves cognition.[9] The mouse work tested manipulations and reported memory and vascular outcomes; the human work measured plasma levels across groups and activity settings.[8,9] Those are different evidentiary lanes. A biomarker association cannot be substituted for an intervention result, and an intervention result in mice cannot supply a human clinical outcome. The combined evidence makes GPLD1 an interesting research target rather than an exercise prescription or a demonstrated means of brain protection.

BDNF, brain-derived neurotrophic factor, presents a related translation problem. Its name sounds almost like an outcome, as though a rise in the

blood must mean that the brain has become more resistant to decline. An October 2026 network meta-analysis pooled 28 studies involving 2,262 people aged 50 or older with mild cognitive impairment. Exercise interventions were associated with increases in *peripheral* BDNF and improvements in depressive symptoms.[10] Those are findings about measured blood levels and symptoms in the included studies, not proof that a change in BDNF caused a cognitive benefit.

The location of the measurement matters. Peripheral BDNF is measured outside the brain; its change does not directly report what happened in a particular brain circuit or whether a participant retained everyday abilities. An exercise intervention can alter many things at once, including physical capacity and mood. If a blood marker and an outcome both change, one has not thereby proved that the marker mediated the outcome. In this analysis, improved depressive symptoms were reported alongside the BDNF finding, while dementia prevention was not established.[10]

The meta-analysis also produced a modeled peak for its BDNF outcome, but the authors described modeled dose points as exploratory predictions, sensitive to the analysis and intended for future trials, not as confirmed clinical optima or evidence of dementia prevention.[10] It would be particularly easy to turn a graph's highest point into a training rule. That would mistake a model of a peripheral marker for a tested clinical prescription. This chapter makes no such conversion.

Other proposed exercise messengers may eventually explain parts of a human effect. Naming a candidate, however, is not the same as demonstrating that altering it protects cognition. As of October 2026, no published human study has shown that exercise protects cognition by changing irisin or clusterin; the GPLD1 and BDNF findings do not establish that link for those pathways either.[9,10] The scientifically useful question is not whether a messenger sounds promising. It is whether human experiments can connect a specific change in that messenger to an outcome that matters, while ruling out simpler explanations.

There is a useful asymmetry here. Mechanistic discoveries can make the small controlled cognitive gains more intelligible, but they cannot enlarge those gains after the fact. Nor can they upgrade observational dementia evidence to a randomized prevention result. The mouse GPLD1 work opens a precise vascular question; the human GPLD1 measurements show how much translation remains.[8,9] The peripheral BDNF synthesis shows that an exercise-related blood response can be measured in people with mild

cognitive impairment, while leaving the brain clinical outcome unresolved.[10]

The September forum thread began with a demand for solid evidence behind proposed neuroprotective agents.[1] Applied evenly, that demand leaves exercise in a stronger position than a mere molecular hypothesis and a narrower position than a proven dementia-prevention treatment. Aerobic and resistance interventions have controlled, small executive-function signals in cognitively healthy older adults; their dementia-prevention grade remains C.[4] HIIT's cognitive-protection grade remains Insufficient because its small randomized literature is inconsistent.[7] Those boundaries do not diminish the people for whom movement is part of a good day. They keep a worthwhile, commonplace intervention from being sold as an outcome no trial here has shown it can deliver.

Chapter 9: The Night Shift: Sleep and the Glymphatic System



On October 9, 2026, RapAdmin opened a forum thread titled “Can we harness the brain’s deep-cleaning system to prevent Alzheimer’s?” The post brought readers to a vivid experiment: a tracer moving through the brain of a sleeping mouse, its flow falling sharply after the animal woke.[1] The image makes the proposed connection between sleep and brain health feel almost visible. It does not show that making a person sleep more deeply will prevent Alzheimer’s disease.

That distinction is the work of this chapter. Researchers can observe fluid movement, record sleep waves, and measure proteins associated with Alzheimer’s pathology. None of those observations is the same as finding fewer cases of dementia among people assigned to a sleep intervention. Nor does an appealing mechanism settle which intervention, if any, improves the process that matters. A reader might reasonably want better sleep without claiming that sleep has become a proven method of brain cleaning. The two propositions can stand apart.

The phrase *deep-cleaning system* compresses several ideas into one reassuring picture. Sleep changes brain activity. Fluids move within and around the brain. Amyloid and tau are proteins of interest in Alzheimer’s research. The tempting next sentence is that sleep can be altered to wash those proteins away and preserve memory. It is also the sentence that requires a human outcome experiment. If that experiment has not been done, or measures only an intermediate signal, the picture must stop where the evidence stops.

This is not an argument against treating disturbed sleep. It is an argument against borrowing certainty from a different question. Obstructive sleep apnea can warrant care for established reasons even when its treatment has not been shown to prevent dementia. A prescription sleeping pill can help with an indicated sleep problem without becoming an Alzheimer's prevention drug. An experimental sound stimulus can change a recording for a moment without showing that a person's thinking will be better years later. Each claim deserves its own test.

What Human Imaging Sees

The attraction of the glymphatic idea is unusually visual. A moving tracer is easier to remember than a hazard ratio, and a pulse of fluid can look like a process being switched on. The term *glymphatic* refers to a proposed route by which fluid exchange participates in clearing material from brain tissue. It gives researchers questions they can investigate. It does not, by itself, identify a validated intervention for people hoping to preserve cognition. Human observations in this area belong, for now, in the imaging and mechanistic lane, not the proven-enhancement lane.[2]

There is a further problem hidden inside the word *clearance*. Seeing fluid enter or move through a space is not necessarily seeing a particular harmful protein leave the brain. A change in the amount of a protein measured at one site could reflect production, redistribution, sampling time, or removal. A scan may faithfully capture a physical event while leaving its biological consequence uncertain. Even if a study can connect a sleep feature to a fluid-flow signal, that connection still needs to survive the next question: did altering the signal improve memory, slow decline, or reduce disease?

In September 2026, Alpha shared an account of pink-noise bursts paired with sleeping brain waves. The excerpt described strengthened slow waves and a brief increase in cerebrospinal-fluid flow on MRI and EEG recordings compared with no sonic stimulation.[3] Those recordings present an intriguing human observation. The word *brief* matters. A fluid-flow difference observed during a recording cannot tell us how much material was cleared over a night, whether the effect recurs over months, or whether an older adult will think more clearly later. The instrumentation is impressive; the clinical question remains open.

AlexKChen's reply in the same discussion offered a counterweight. He described the possible effect as weak and noted that sound out of phase with sleep waves could disturb sleep.[4] His assessment is forum

commentary, not a clinical result. Still, it identifies a real design problem: an intervention intended to improve one aspect of sleep might degrade another. A louder or more elaborate signal could produce a larger laboratory response and a worse night's rest. The endpoint chosen for a study would determine whether that tradeoff is even noticed.

For how sleep sits alongside stress and recovery in a broader health framework, see Book One, *The Longevity Operating System*, Chapter 7, "Sleep, Stress, and Recovery."

The image-to-outcome gap is not a technicality imposed to spoil a promising idea. It protects the distinction between discovering a mechanism and improving a life. Investigators may first need to learn how fluid movement differs across sleep states, ages, and health conditions. That work can sharpen later trials. But a person deciding what to believe about dementia prevention needs another kind of evidence: an intervention compared fairly with a control, followed long enough to show a meaningful cognitive or disease outcome. Imaging may help explain such a result once it exists. Imaging alone cannot substitute for it.

One might imagine an apparently clean sequence. An intervention increases slow waves; a scan shows more fluid movement; a blood marker shifts; cognitive testing improves. Each arrow has to be established rather than assumed. The first change might be reliable while the second varies from night to night. The blood marker might change for reasons unrelated to brain clearance. A short cognitive test might improve through familiarity. And even a genuine memory gain during a trial would not automatically demonstrate fewer future dementia cases. Trials that measure several links can reveal where a proposal succeeds and where it fails.

Observational genetics offers a different view of sleep that is easy to overread. A 2026 UK Biobank analysis developed a polygenic score using wearable-derived sleep-duration data from 77,770 participants, then tested it in an independent sample of 264,746; there were 1,451 Alzheimer's cases over a median 12.5 years.[5] People in the highest rather than middle fifth of the score, corresponding to about 15 minutes of longer *predicted* sleep per day, had a lower recorded Alzheimer's risk: hazard ratio 0.79, with a 95 percent confidence interval of 0.67 to 0.94.[5] The result connects inherited predictors of sleep duration with later disease risk. It does not show what would happen if people were made to sleep longer, nor does it establish that glymphatic flow carried the association.[5]

That difference between a predictor and an intervention is particularly important for sleep. People who sleep poorly may differ in health, work, pain, medication use, or early disease processes. A genetic score reduces some familiar sources of confounding but introduces its own interpretive questions: inherited variants can influence more than one trait, and predicted sleep duration is not the same thing as a prescribed change in actual sleep. Neither a cohort of sleepers nor a picture of moving fluid gives a clinician a dementia-prevention treatment to offer on that basis alone.

On the series evidence scale, C means observational or uncontrolled human data; D means preclinical evidence only. For the headline claim that glymphatic "enhancement" prevents dementia or slows decline in at-risk adults without dementia, the grade is Insufficient: human imaging observations and laboratory work do not establish that an enhancement intervention achieves that outcome.[2] The grade attaches to the prevention claim, not to whether studying brain-fluid exchange is worthwhile.

Apnea and an Uneven Record

Sleep apnea brings the discussion out of the scanner and into a well-recognized medical condition. Repeated breathing interruptions can fragment sleep; continuous positive airway pressure, or CPAP, is used to treat obstructive sleep apnea. It is plausible to ask whether reducing those interruptions might also help protect cognition. Plausibility is not a dementia result. The relevant distinction is between treating apnea for its established indications and advertising treatment as protection against a disease it has not been shown to prevent.

A multicenter randomized trial published in 2025 assigned 148 cognitively normal adults with obstructive sleep apnea, defined for entry by an apnea–hypopnea index of at least 15 events per hour, to CPAP plus best supportive care or best supportive care alone. The planned intervention lasted 12 months; 124 participants completed that interval. Researchers assessed cognitive performance and neuroimaging biomarkers.[6] Random assignment makes this a more direct test of the assigned treatment than an ordinary comparison of people who did or did not use CPAP. Its size, duration, completion count, and endpoints also set limits on what can be concluded from it.

Most obviously, a 12-month study of 148 cognitively normal participants was not a demonstration that CPAP prevents dementia.[6] The published study examined cognitive performance and neuroimaging biomarkers, but

those measures cannot by themselves establish dementia prevention.[6] Even a favorable shift in a scan would require a separate argument to connect it to lasting cognitive benefit. Conversely, the absence of a persuasive dementia endpoint in a study this small and short would not prove that no longer-term benefit is possible. The honest inference is narrower than either slogan.

Adherence adds a complication common to trials of treatments people must use repeatedly. An assignment to CPAP is not the same as uninterrupted exposure to effective treatment. Those who tolerate and continue a device may differ from those who do not, including in ways related to health. An analysis limited to enthusiastic users risks losing some of the protection provided by random assignment; an assignment-based analysis may answer a more practical question but show a diluted effect if use varies. Neither approach makes a brief imaging change equivalent to dementia prevention.

The Danish registry study provides a useful contrast. Published in August 2025, it matched 62,928 people with diagnosed obstructive sleep apnea to 62,928 comparison participants. Median age was 52, and 76 percent were male.[7] Its scale gives it a view of recorded diagnoses that a small randomized trial cannot provide. Yet scale cannot randomize who develops apnea, who receives a diagnosis, or who uses CPAP. The registry answers an association question under the conditions of care recorded in Denmark, not the question of what would happen if otherwise comparable people were assigned different treatments for many years.

Against the matched comparison group, the estimated hazard ratio for all-cause dementia among those with apnea was 1.10, with a 95 percent confidence interval of 0.98 to 1.24. For Alzheimer's disease it was 1.16, with a confidence interval of 0.94 to 1.43. Both intervals included the null value of 1.00.[7] Those figures neither establish an increased risk in this analysis nor establish that the risk is exactly the same. They describe modest, uncertain associations in the observed population. Turning them into a declaration that apnea causes Alzheimer's would discard the uncertainty; declaring the question settled in the other direction would do the same.

In subgroup analyses, the association was attenuated among people treated with CPAP.[7] That is the line most likely to travel farthest, because it seems to complete a satisfying story: apnea raises risk, treatment removes risk. But treatment was not randomly assigned in the cohort. People recorded as receiving CPAP may differ from others in access to care, symptom severity,

follow-through, other diagnoses, and opportunities to have dementia detected. Statistical matching can address measured differences, not every difference that matters. The subgroup finding cannot show that CPAP caused a reduction in dementia risk.[7]

The two studies therefore correct different exaggerations. The Danish cohort does not allow a causal promise about CPAP, while the randomized study does not provide a long-term dementia outcome.[6,7] They are not competing votes to be averaged by intuition. One supplies reach across a large clinical population and remains vulnerable to treatment-selection bias. The other supplies random assignment over a limited period and cannot tell us whether dementia incidence changes over years. Reading both is more informative than choosing the one whose format or result seems most reassuring.

There is also a population question. The Danish cohort's median age of 52 means its recorded associations cannot be assumed to describe precisely the risk facing a reader decades older.[7] The randomized study enrolled cognitively normal adults with a specified degree of apnea, not a representative group of everyone troubled by sleep or worried about memory.[6] Differences in age, underlying health, and outcome measurement can alter what a result means. "People with sleep apnea" is not one uniform research population, and "brain health" is not one endpoint.

The evidence-grade headline for sleep-apnea treatment with CPAP is C for dementia. On the series scale, C denotes observational or uncontrolled human evidence; the randomized cognitive and imaging study does not establish dementia prevention.[6,7] The medical reason to address apnea need not wait for that claim. CPAP can be discussed for apnea's established indications without presenting it as an Alzheimer's prevention prescription. The distinction honors both ordinary clinical care and the unresolved research question.

A Sleeping Pill's Surrogate

Another attractive sleep story begins with a drug rather than a device. Suvorexant is an orexin-receptor antagonist used as a prescription hypnotic. Reports of short-term changes in amyloid and tau measures have made it interesting to researchers studying sleep and Alzheimer's biology. The finding belongs in the surrogate lane: a protein measure can suggest an effect worth examining, but it is not a count of prevented dementia cases. Suvorexant is not approved for Alzheimer's prevention.[2,8]

A surrogate is most useful when it reliably predicts the clinical outcome of interest under intervention. Without that validation, even a change in the hoped-for direction can mislead. Suppose a measured amyloid-related signal falls after a night of altered sleep. That could represent a favorable change in a disease process, a temporary redistribution, or a shift whose long-term significance is unknown. The measurement may be real without serving as a verdict. The same caution applies to tau: the name of a disease-associated protein does not make every short-term movement in its measured level a disease outcome.

Sleep drugs pose an additional interpretive difficulty. A person can report sleeping better while aspects of sleep architecture or next-day functioning change in less welcome ways. A drug's effect on a laboratory marker may not track how rested or clear-headed a person feels, and either of those experiences may fail to predict cognitive health years later. The relevant trials must assess benefits and harms in the population and timescale named by the prevention claim. A brief biological experiment cannot do that work on its own.

SToP-AD, the Sleep Trial to Prevent Alzheimer's Disease, is designed to move beyond the short-term signal. Its registry describes a phase 2 study with estimated enrollment of 120 participants with poor sleep, comparing suvorexant with placebo over 18 to 24 months. The listed primary outcome is change in amyloid accumulation measured by the plasma pT217/T217 ratio.[8] That design can test whether the drug changes the specified marker over a much longer period than a brief experiment. It still does not make a marker change identical to prevented dementia. The registry is a plan, not an efficacy report.[8]

As of October 2026, the SToP-AD registry lists the study as recruiting, with no efficacy result reported.[8] The distinction between a registry entry and a result can seem obvious until a trial title does the rhetorical work. "To Prevent Alzheimer's Disease" states what investigators hope to learn, not

what has already been demonstrated. An estimated enrollment describes an intention, not necessarily the eventual analyzed population. A primary biomarker endpoint tells readers what the experiment can most directly answer.

The headline grade for orexin antagonists is Insufficient for prevention. Reported short-term amyloid and tau changes may constitute a controlled human surrogate signal, but they do not establish protection against cognitive decline or dementia; the longer SToP-AD study has not reported efficacy results.[2,8] This is not a judgment that a hypnotic cannot be useful for its approved purpose. It is a boundary around a different claim. A short-term protein shift does not support prescribing a drug for dementia prevention.

The boundary also prevents a common comparison error. If one study examines a prescription drug, another examines CPAP, and a third records an imaging response to sound, their results do not form a ranking of "best brain cleaners." They involve different participants, interventions, controls, and endpoints. One might measure a protein, another cognitive performance, another moving fluid. Until studies connect these measurements to outcomes under well-tested interventions, placing them on a single scale would convey precision the field has not earned.

Experiments Still in the Night

ALPS, the Alzheimer's Pathways Sleep Study, asks a more direct question about changing slow-wave sleep. A protocol published in February 2026 describes a planned randomized trial targeting 116 adults aged 65 to 85 with poor sleep. Its intervention arm is designed to increase slow-wave activity through a four-week sleep-schedule intervention, against an attention-matched comparator. Planned outcomes include hippocampal activity, plasma amyloid-β, and overnight memory retention.[2] Those are meaningful choices for an experiment: a comparison group helps separate an intervention's effect from attention, expectation, and the passage of time.

They are not, however, reported benefits. ALPS is a protocol, not a paper showing that the intervention improved memory or amyloid measures.[2] And its planned outcomes differ from the chapter's hardest question. Overnight retention can indicate whether learning was preserved across a night; it is not dementia incidence. Hippocampal activity can help researchers study a proposed pathway; it does not by itself show that daily

function is protected. Plasma amyloid-β may be informative while remaining an indirect measure of a long disease process. A well-designed early experiment can be valuable precisely because it does not pretend to have finished the inquiry.

As of October 2026, the ALPS publication is a trial protocol, not a report of efficacy results.[2] SToP-AD likewise remains a trial plan rather than evidence of prevention.[8] These studies ask different questions about sleep, memory, and Alzheimer's-related biomarkers. Results may eventually clarify whether the interventions change those measures. Neither protocol shows that the intervention works.

The forum's pink-noise discussion shows why experiments like these matter. Alpha's September post offered a compelling account of slow waves and fluid flow seen during stimulation.[3] AustraliaLongevity answered with restraint, writing, "We need more data before doing things this precise."[9] The exchange captures two reasonable responses to an early signal: interest in what a recording shows, and reluctance to turn it into a personal clearance strategy. Pink noise and other forum claims about clearing proteins remain hypotheses pending convincing clinical outcomes.

Even an apparently harmless sound intervention can fail in more than one way. It might produce the intended brain-wave pattern only in a narrow laboratory setting. It might alter a fluid-flow measurement without removing a harmful substance. It might improve one night's recording and disrupt sleep on another. It might help a selected group yet disappoint in older adults with fragmented sleep or other illnesses. These possibilities do not make the experiments futile. They explain why the control condition, repeated measurements, participant experience, and eventual cognitive outcomes all matter.

The forum had another thread about a possible "fast lane and slow lane" for clearing waste. JazzMann saw value in developing ways to test interventions rather than merely assuming that they improve glymphatic function.[10] That is a productive standard for a community that reads early research closely. Better measurement could expose weak claims as well as support strong ones. A future method that distinguishes ordinary fluid movement from meaningful removal of material would improve experiments. It would still need to be linked to outcomes before becoming a prevention promise.

There is a familiar lure here: if sleep supports repair, surely more of a sleep-related signal must be better. Biology seldom offers so simple a dial.

Total sleep time, slow-wave activity, continuity, breathing, comfort, and next-day functioning can move differently. A person might spend longer in bed without sleeping better. A stimulus might amplify a measured wave while becoming an unwelcome interruption. A sedating drug might improve one sleep complaint without establishing an advantage for memory. The only defensible claim is the one attached to the endpoint actually tested.

This chapter's strongest conclusion is therefore deliberately limited. Human imaging and mechanistic observations give investigators plausible targets to study; ALPS is designed to test several such measures.[2] The Danish apnea cohort offers uncertain associations and an observational CPAP subgroup finding, while the randomized CPAP study cannot establish dementia prevention.[6,7] Short-term protein changes associated with suvorexant remain surrogates, and SToP-AD and ALPS have not reported prevention results.[2,8] As of October 2026, no published sleep-intervention result cited here establishes that altering sleep prevents dementia in at-risk adults without dementia; the genetic association with longer predicted sleep does not answer that treatment question either.[2,5,6,7,8]

A separate question arises whenever a familiar sleep-related supplement is presented as a brain-protection product. For the melatonin correction, see Chapter 20. It would be a mistake to fill the evidence gap here with a different substance simply because its name is associated with sleep.

The October forum question deserved an answer rather than a dismissal. The sleeping-mouse tracer, the human fluid-flow recording, and the plans for longer trials each show researchers finding more precise ways to ask what happens at night.[1,2,3,8] Their images are not empty. They are also not clinical outcomes. For now, the brain's proposed cleaning system is a subject of investigation, apnea treatment stands on its established indications, and Alzheimer's prevention remains a claim that sleep experiments have yet to earn.

Chapter 10: Signals In: Hearing, Vision, and the Trained Brain



On August 1, 2026, RapAdmin posted a summary of a conversation with the Sherzais. Its central claim was that Alzheimer's disease and vascular dementias develop over years rather than arriving suddenly when symptoms become visible.[1] That long view makes an ordinary question unexpectedly difficult. If a person begins hearing conversations clearly again, and another person practices a computer task that asks for faster visual responses, have they done the same kind of thing for the brain?

Both activities change experience. Neither is equivalent to removing Alzheimer's pathology. Hearing correction may restore access to speech, social exchange, and everyday information that were already present but difficult to receive. Cognitive training asks someone to improve performance under deliberately designed conditions. Vision correction raises a third possibility: making the world legible again might alter what a person can do without directly changing the disease processes that can impair memory. These are plausible ideas, not interchangeable findings.

The distinction matters because sensory impairment can also distort a cognitive test. Someone who mishears instructions or cannot see a stimulus clearly may perform poorly for reasons that are not dementia. Restoring access can improve the fairness of an assessment, the ease of daily life, or both. A trial that measures cognitive change must still ask whether it has detected a durable change in thinking rather than a change in how well its questions reach the participant.

This chapter follows two questions about incoming signals, hearing and vision, before turning to an unusually specific result from a training trial.

Its ending is less tidy than a slogan about “using the brain.” What matters is which population was studied, which task or aid was tested, and whether the measured result was cognition, a dementia diagnosis, or simply better access to the world.

The Hearing Trial's Two Stories

A hearing aid addresses an identifiable problem: sound reaching a person does not yield speech that is reliably understood. That makes hearing correction different from asking an otherwise accessible brain to become faster at a novel task. Yet the proposed connection to dementia is not fanciful. Hearing difficulty can make conversation effortful; withdrawing from conversation may change daily cognitive demands; and a shared cause could contribute to both hearing loss and later cognitive impairment. Those explanations do not predict the same trial result. Only some imply that correction itself will reduce dementia risk.

ACHIEVE is best read as two stories, not one victory or one dismissal. In its primary randomized comparison, hearing intervention did not significantly slow cognitive decline in the full study population. A higher-risk subgroup showed a signal of benefit. The first finding governs the overall claim: the trial did not establish a general cognitive-prevention effect for everyone enrolled. The second warrants further study, particularly because an intervention could plausibly matter more when participants face a greater initial risk. A subgroup result, however, cannot quietly replace a null primary result as the trial’s headline.

There is a practical reason the two stories are easy to collapse. Hearing correction has benefits that need no dementia-prevention claim. Understanding a family member, following a discussion, or hearing a warning signal can matter immediately. Those benefits may make the higher-risk signal seem more persuasive than the evidence alone permits. Conversely, the null primary result does not make restored hearing pointless. It says something narrower and more rigorous about the cognitive outcome tested in the full randomized group.

For the grade table, hearing correction receives a C headline for preventing dementia or slowing decline in at-risk adults without dementia: C denotes observational or uncontrolled human evidence for that broad claim. The B-null primary trial finding denotes controlled evidence of no effect on the overall cognitive endpoint tested, while the higher-risk subgroup remains a

controlled signal with limits. The grade is not a rating of whether hearing clearly is worthwhile. It specifies what the prevention claim has earned.

A second randomized trial arrived with a different question. Published in September 2026, CHOICE enrolled 703 adults in Shanghai who were at least 60 years old, already had mild cognitive impairment, and had moderate-to-severe hearing loss. Participants were assigned to a hearing intervention or hearing-care education. At 24 months, dementia-level impairment occurred in 3.09% of the intervention group and 4.74% of the education group; the difference was not statistically significant.[2] The numerical gap should not be presented as proven protection simply because it points in a favorable direction.

CHOICE does not repeat ACHIEVE in another city. Its participants already had MCI, its comparator was hearing-care education, and its reported endpoint was dementia-level impairment over two years.[2] A trial among people with MCI cannot answer whether correcting hearing prevents dementia in cognitively healthy adults. It can test an important adjacent claim, and on this endpoint it did not establish a benefit. Keeping those questions separate avoids a common error: combining unlike populations and outcomes into an apparently stronger “hearing trials” verdict.

Now set the randomized findings beside a result that looks more decisive at first glance. A January 2026 observational study used ASPREE and ancillary-study data to emulate a trial of hearing-aid prescription. Across imputed analyses, the median eligible sample was 2,777 people, with a mean age of about 75. Estimated seven-year dementia risk was 5.0% under a prescription strategy and 7.5% without one, a relative risk of 0.67. Estimated overall cognition, however, was similar between strategies, with a mean difference of 0.03 standard deviations. The authors warned that residual confounding could remain.[3]

Those figures deserve their full shape. The estimated absolute dementia-risk difference is 2.5 percentage points over seven years, while the relative comparison describes roughly one-third lower risk under the modeled prescription strategy.[3] An emulation can carefully align eligibility, follow-up, and analysis with a hypothetical trial. It still cannot randomly allocate the reasons people received hearing aids. Access to care, willingness to seek help, other health differences, and factors that were imperfectly measured could influence both prescription and later diagnosis. Residual confounding is not a ritual caveat appended to an

otherwise randomized result; it is the central uncertainty when interpreting this estimate as a causal effect.

A March 2026 review gives further reason to take the association seriously without declaring the question settled. Across 46 studies involving 231,565 participants, hearing-aid use was associated with better global cognition and memory and with a lower risk of cognitive impairment. The reported pooled relative risk for cognitive impairment was 0.84. These are pooled associations, not proof that an aid caused prevention.[4] Many participants and a consistent direction can strengthen confidence that a relationship exists. They do not, by themselves, identify which way causation runs or how much of the relationship correction explains.

Consider an older adult whose hearing becomes poorer gradually. She may miss fragments of conversation, then speak less often in groups because repeatedly asking for clarification is tiring. A hearing intervention might change that experience substantially without producing a measurable dementia effect during a trial's follow-up. Another participant may receive an aid but gain little access to conversation for reasons unrelated to the device. A third may have cognitive impairment that makes managing any new piece of equipment difficult. None of these sketches is an outcome from ACHIEVE or CHOICE; they show why an intervention delivered to the ear does not impose one uniform change on a person's life.

The evidentiary challenge is therefore more precise than "does hearing matter?" Hearing loss is associated with later cognitive impairment, and hearing correction can address hearing.[4,5] Whether correction changes a dementia trajectory, for whom, and on which measure remains less certain. ACHIEVE's primary result restrains the broad claim; its subgroup signal leaves a narrower question open. CHOICE adds a null result in people who already had MCI. The ASPREE emulation suggests a favorable seven-year dementia association while finding little difference in overall cognition, but it remains observational.[2,3] Treating these as separate pieces of evidence is not excessive caution. It is how their differing findings can be useful.

Vision and the Missing Trial

The corresponding vision question is almost irresistible. If an older adult cannot see a page, recognize a face at a distance, or make out an object on a cognitive test, what changes when sight improves? As with hearing, better access to the world is meaningful on its own terms. The further claim, that correcting vision prevents dementia, requires evidence about that outcome.

A 2026 systematic review and meta-analysis gathered 62 studies of visual impairment, hearing impairment, or both in relation to dementia or cognitive impairment. Its pooled association with dementia was an odds ratio of 1.60 for visual impairment, 1.26 for hearing impairment, and 1.66 for dual sensory impairment. The included studies varied, and some were cross-sectional rather than longitudinal. The authors did not establish that correcting either impairment would prevent dementia.[5] An association between poor vision and dementia can reflect several paths: visual loss might reduce activity or contact with others; emerging cognitive difficulty might make an impairment harder to identify or manage; and other health conditions might influence both. A pooled number does not sort those paths into causal shares.

Cataract surgery brings the question into sharper focus because it changes an identifiable visual obstruction. Observational studies of cataract surgery have reported associations with dementia outcomes, but the comparison between people who undergo surgery and people who do not is vulnerable to differences that precede the operation.[6] The person able to arrange and complete surgery may differ in health, support, access to care, or early cognitive status from the person who does not. Statistical adjustment helps only for differences it can adequately measure. Even if surgery greatly improves vision, a dementia-prevention effect does not follow automatically.

The World Health Organization's second-edition dementia-risk-reduction guidelines, published in July 2026, drew a firmer boundary around that inference. For dementia-risk reduction specifically, WHO found insufficient evidence to recommend vision-impairment interventions. The evidence it reviewed was limited to observational cataract-surgery studies in adults with normal cognition, and its certainty about dementia-risk effects was very low.[6] This is not a recommendation to leave vision impairment uncorrected. It is a judgment about the evidence needed to make *dementia prevention* the reason for an intervention.

As of October 2026, the 2024 Lancet Commission's list of modifiable dementia risk factors includes untreated vision loss. A risk-factor designation and a successful correction trial answer different questions. The first asks whether an exposure is associated with population risk under a set of modeling assumptions; the second asks what happens when people are assigned an intervention that changes that exposure. The gap is especially important for conditions entangled with health-care access.

"Modifiable" describes something that can, in principle, change. It does not certify how much later dementia risk changes when it does.

Cataract surgery and vision correction therefore receive a C grade for the dementia-prevention headline: the available human support is observational, and WHO judged it insufficient for a recommendation specifically to reduce dementia risk.[6] That grade should not be mistaken for a verdict on visual function. A person can have an excellent reason to value clear sight even if no trial has shown that restoring it prevents Alzheimer's disease.

Measurement creates one more complication. Suppose an intervention enables someone to see the symbols on a cognitive test for the first time. A higher score afterward could reflect improved access to the test, improved performance in ordinary life, a change in cognition, or some combination. That ambiguity is not an argument against measuring cognition; it is a reason to design assessments that do not confuse sensory access with the capacity being assessed. Hearing studies face a parallel problem when spoken instructions form part of testing.

There is also a genuine human cost to reducing the subject to a dementia endpoint. Corrected vision may change reading, movement, confidence outdoors, or recognition of people nearby. Those outcomes should not have to borrow credibility from a speculative prevention effect. The sober position is neither "vision does nothing for the brain" nor "vision correction prevents dementia." It is that the demonstrated case for visual access and the unproved case for dementia prevention occupy different evidentiary ground.

For the distinction between established prevention and plausible but unconfirmed prevention claims, see Book One, *The Longevity Operating System*, Chapter 15, "Dementia Prevention Without Magical Thinking."

ACTIVE's One Durable Arm

Hearing and vision interventions improve a channel through which information enters. Cognitive training changes something else: performance on an activity a person repeatedly practices. Its central question is transfer. Does becoming faster or more accurate at the training task improve ordinary thinking, and does any such improvement translate into fewer dementia diagnoses years later?

The ACTIVE study offers an unusually long view, but also a lesson in narrow claims. It enrolled 2,802 adults in 1998–99 and compared memory training, reasoning training, speed-of-processing training, and a control condition. A Medicare-linked analysis followed dementia diagnoses for up to 20 years. The reported long-term signal appeared in the speed-training group that also received booster training, not in speed training without boosters, memory training, or reasoning training.[7] Calling this a result for "brain games" would erase the trial's most informative distinction.

In the reported speed-with-boosters comparison, 105 of 264 participants, about 40%, were diagnosed with dementia, compared with 239 of 491 controls, about 49%. The hazard ratio was 0.75, with a 95% confidence interval of 0.59 to 0.95.[7] On those reported group proportions, the absolute difference was about nine percentage points; the hazard ratio expresses a relative difference in the rate of diagnosis across follow-up, not a promise that any individual's risk falls by exactly one quarter.[7] Both descriptions belong in the account. The relative figure communicates the modeled contrast; the absolute figures show how often the recorded outcome appeared in these particular groups.

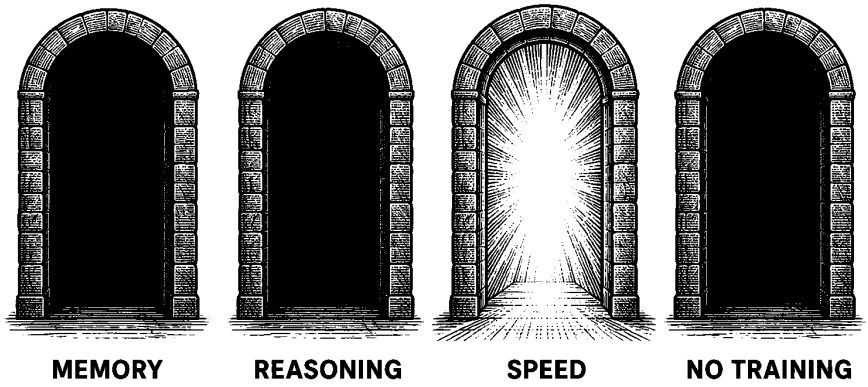


Figure 9. ACTIVE at twenty years. Of the three training arms, only speed-of-processing training was associated with fewer dementia diagnoses in Medicare claims, and the signal was concentrated among participants who received booster sessions. Memory and reasoning training showed no such association.

The follow-up is striking precisely because most training claims stop at a post-training test. Twenty years is long enough to ask whether a laboratory exercise has any detectable relation to a clinical outcome much later.[7] Yet length of follow-up does not make an endpoint immune to error. Medicare-linked diagnoses are claims-based outcomes: they depend in part on whether dementia is recognized, documented, and coded. They are not the same as every participant receiving an identical, repeated clinical evaluation for dementia across two decades. The study supports a signal in the recorded outcome; it does not reveal every case that was missed or establish the biological route from training to diagnosis.

The boosters matter, too. One interpretation is that continued practice was needed to maintain a useful skill. Another is that the booster subgroup differed in engagement or opportunity in ways that deserve close attention when interpreting a long-term comparison. The reported signal was specific to speed training with boosters; speed training without them showed no significant effect.[7] That pattern does not establish a general rule about how much practice anyone should do. It confines the result to what was actually observed.

ACTIVE earns B, narrowly defined, on the chapter's grade scale: a controlled human signal with limits for speed-of-processing training with boosters and a Medicare-linked dementia outcome. Memory and reasoning training in the reported analysis did not show a statistically significant dementia-incidence effect, nor did speed training without boosters.[7] Those tested arms merit B-null for that endpoint, meaning controlled evidence of no demonstrated effect on the outcome tested, not proof that practicing memory or reasoning has no possible value for any purpose.

The temptation to broaden the claim is understandable. A person who gets quicker at a visual task feels quicker. Computer programs can display scores to several decimal places, creating an impression of precision that a later-life outcome cannot match. But improvement on a practiced task is the result one would expect from practice. Generalization requires a separate test. A participant might become exceptionally good at identifying fleeting objects on a screen while remaining unchanged on measures that matter in daily life. Conversely, a small change in attention or response speed might have consequences a short standard test misses. Neither possibility licenses a product-wide claim from ACTIVE's one positive arm.

The control group is part of the story as well. Training studies can differ in how much attention, instruction, novelty, and social contact participants

receive. If the intervention group spends time with instructors while controls do not, the resulting contrast may not isolate the cognitive task. ACTIVE's long-term signal identifies a specific randomized training comparison; it does not prove that every possible ingredient worked independently.[7] A claim that social interaction produced the result would need its own comparison, just as a claim about speed practice does.

Nor should ACTIVE be folded into the broader evidence on multidomain lifestyle programs as though those studies isolated cognitive training. FINGER reported improvement in a cognitive composite after a two-year program combining several activities, while US POINTER found a greater global-cognition improvement with a structured program than with a self-guided one; US POINTER did not test dementia incidence. Those findings can support questions about comprehensive programs. They cannot assign the observed gains specifically to training exercises or social contact.

ACTIVE consequently occupies an unusual middle position. Its reported dementia association comes from random assignment to a particular training arm, which is stronger than a simple comparison of people who choose games and people who do not. Its long-term outcome comes from claims, and the signal is confined to the speed-plus-boosters group.[7] The fairest description is not "training prevents Alzheimer's" or "brain training failed." It is that one defined approach produced a controlled, long-term signal worth taking seriously without promoting all cognitive exercises by association.

Reserve Is Not a Score

The word *reserve* gives these findings a possible framework, but it can also blur them. Cognitive reserve describes the observation that people may show different levels of thinking and function despite measures of brain pathology that appear similar. It does not mean that someone has a hidden tank of points that can be filled by an app, a conversation, or a better pair of glasses. Nor does it mean pathology stops developing when performance remains good.

A study published in October 2026 examined education, cognitive performance, and markers of brain pathology in PREVENT-AD and CIMA-Q cohorts. Higher education was generally associated with better cognitive performance even after adjustment for MRI and plasma markers. The relationship was more consistent for baseline cognitive level than for

subsequent cognitive change, and longitudinal findings varied across cohorts.[8] That pattern is compatible with some people performing better at a given measured level of pathology. It is not evidence that adding a short course of training in later life reproduces the consequences of years of education, or that education prevents the underlying pathology.

Reserve also complicates the meaning of a diagnosis date. If a person functions well for longer despite accumulating disease, symptoms might become apparent later without disease having been prevented. A 2025 meta-analysis of bilingualism illustrates the distinction. Across studies of symptom onset, bilingual participants were on average 3.45 years older when dementia symptoms began than monolingual participants. The studies of dementia incidence, however, did not provide convincing evidence that bilingualism prevents dementia.[9] Later observed onset and lower lifetime incidence are different outcomes. Differences in education, migration, social setting, and how symptoms are noticed can further complicate a simple causal story.

Something similar occurs when "staying connected" is offered as a substitute explanation for every sensory or training result. Social contact can be valuable without proving a dementia-prevention effect. In a cohort of 8,189 adults aged 65 or older observed across waves from 2013 to 2022, moderate-to-high digital isolation was associated with higher dementia risk than low digital isolation; the adjusted hazard ratio was 1.36. The analysis accounted for several measured factors, but it could not establish that adding digital engagement would prevent dementia.[10] People may become digitally isolated because of emerging impairment, because of other health or access barriers, or for reasons the data did not fully capture.

An intervention study can clarify a social claim only if it measures the claimed outcome. A Hong Kong trial randomized 245 lonely community-dwelling adults aged 60 or older to mindfulness training or a social-contact control. At 12 months, mindfulness was not superior to social contact for the primary loneliness outcome, although loneliness improved within both groups. The trial reported no dementia or cognitive-decline result.[11] It says something about loneliness under those conditions. It cannot be enlisted as evidence that either intervention prevents dementia.

Other cognitive training and social-contact claims are B-null where a controlled trial tested a specified claim and found no effect on its endpoint; otherwise they are claim-specific C or Insufficient. ACTIVE's memory,

reasoning, and speed-without-boosters arms provide the narrow B-null dementia findings. The digital-isolation association is C for the relationship it observed, not a trial of social contact. The loneliness trial cannot grade a dementia-prevention claim it never measured.[7,10,11] Grades remain attached to sentences that can be tested, not to an appealing category called "keeping the mind active."

There is a further risk in treating reserve as a score: it can turn uneven opportunity into a morality tale. Education, usable hearing and vision, time for leisure, and access to other people are not distributed equally. If people with more of those resources perform better on cognitive tests, it would be a mistake to conclude that those who perform worse failed to exercise their brains. The reserve concept can help explain variation in observed function. Used carelessly, it can hide variation in what people have been able to learn, hear, see, and do.

It can also obscure the difference between performance and pathology at the moment a person seeks help. Better hearing may let a person understand a question. Better sight may let her see it. Practice may make her faster on a related task. Education or experience may help her solve an unfamiliar problem. These effects can matter greatly while leaving open whether amyloid, tau, vascular injury, or other processes have changed. The strongest version of a reserve claim would measure both function and disease over time, then show exactly how an intervention altered their relationship. The evidence here does not justify assuming that result.

Return, then, to RapAdmin's long-timescale post.[1] A process that may be under way well before symptoms does not make every activity performed in those years a prevention treatment. It makes careful distinctions more valuable. ACHIEVE offers a null overall cognitive result and a higher-risk subgroup signal; CHOICE supplies a separate null comparison among people with MCI; observational hearing studies remain suggestive but cannot remove residual confounding.[2,3] Vision impairment tracks dementia risk, while WHO finds the intervention evidence insufficient for a dementia-prevention recommendation.[5,6] ACTIVE contributes one long-term, narrowly defined speed-training signal, not a license to generalize from practice to every "trained brain."[7]

Repairing an incoming signal and practicing a cognitive task are therefore not the same kind of intervention. One changes access to information; the other asks a person to acquire or maintain a skill. Either may improve daily experience, and each deserves outcomes suited to its purpose. Whether

either also changes the course of dementia is a separate question, to be answered without confusing clearer hearing, sharper sight, a higher test score, and less disease.

Chapter 11: Hormones and the Critical Window



On September 19, 2026, RapAdmin opened a forum thread whose title announced “Targeted Dementia Protection in Critical 46 to 56 Age Window.”[1] The post described an analysis of 183,450 postmenopausal women in the UK Biobank and said hormone therapy was associated with a 10% lower risk of all-cause dementia, with larger apparent benefits in particular subgroups.[1] A second post gave a headline estimate: a hazard ratio of 0.90 for all-cause dementia among hormone-therapy users.[2]

Four months earlier, on May 30, the same handle had posted a different possibility. An analysis of 10,978 postmenopausal women, RapAdmin wrote, linked later menopause with better late-life performance on some cognitive measures while finding no general cognitive benefit associated with a history of hormone therapy.[3] John_Hemming offered an interpretation: “if a woman is aging more slowly that will affect both menopause and the development of cognitive issues.”[4]

Both threads ask a question worth taking seriously. Does exposure to hormones around menopause affect the aging brain? They also illustrate why an association can be difficult to read. Age at menopause, reasons for using therapy, age when therapy begins, and later cognitive health may travel together without any one of them being the cause of the others. A compelling subgroup result does not resolve that problem merely by having a narrow age range attached to it. Nor does the possibility that later menopause marks something else about aging prove that hormone therapy has no effects.

The phrase *critical window* gives the debate its shape. It proposes that a treatment begun near menopause might have different consequences from the same broad category of treatment begun decades later. That is a plausible question about timing, not an established dementia-prevention claim. To see why, it helps to put the evidence in chronological order: first the randomized trials that began in older women, then a randomized trial that began near menopause, then the later observational studies and regulatory change. The men's evidence follows a similar rule: identify the cognitive test actually performed before drawing a conclusion from a hormone result.

Starting Late: WHIMS

The Women's Health Initiative Memory Study, or WHIMS, remains the clearest reason not to speak casually of menopausal hormone therapy as brain protection. In its estrogen-plus-progestin trial, participants were at least 65 years old when they entered the study. Over a mean follow-up of about four years, probable dementia occurred at a rate of 45 versus 22 cases per 10,000 person-years in the hormone and placebo groups. The hazard ratio was 2.05, with a 95% confidence interval of 1.21 to 3.48.[5] Put in absolute terms, that was about 23 additional probable-dementia cases per 10,000 women per year in the population and period tested.[5]

The distinction between a rate and a forecast for one person matters. The WHIMS result describes groups of women who entered a particular trial at 65 or older; it does not tell an individual reader what will happen to her. It does, however, establish a controlled human harm signal that cannot be set aside because another study later found a favorable association. The trial also found no significant difference in mild cognitive impairment, with a hazard ratio of 1.07.[5] An unchanged MCI result does not cancel the increased probable-dementia result. The two outcomes were measured separately, and the dementia finding is the reason the older-start population needs its own evidence lane.

A hazard ratio near two can sound as though dementia became nearly inevitable. The absolute rates show something different: probable dementia remained uncommon during the trial, while occurring substantially more often in the treatment group.[5] Relative and absolute descriptions are both necessary. The relative estimate conveys the strength of the comparison between groups; the additional cases per 10,000 women per year convey its

scale in the population studied. Neither number should be detached from the older age at entry.

WHIMS also studied estrogen alone in women who had undergone hysterectomy. In that trial, the probable-dementia hazard ratio was 1.49, but its 95% confidence interval of 0.83 to 2.66 included no difference. When the estrogen-alone and estrogen-plus-progestin trials were pooled according to the study plan, the probable-dementia hazard ratio was 1.76, with a confidence interval of 1.19 to 2.60.[6] It would flatten the evidence to call every WHIMS regimen equally proven to double dementia risk. It would be equally misleading to present the nonsignificant estrogen-alone estimate as reassurance that starting hormone therapy after 65 protects the brain.

What changed in WHIMS was not simply a laboratory measure or a questionnaire score. Its troubling outcome was probable dementia in women who started therapy at older ages.[5,6] That lends the finding clinical weight. But the trial was not a test of therapy begun near the last menstrual period. A woman beginning treatment in her early fifties would differ from a WHIMS participant by age and by the length of time since menopause. Projecting the trial's hazard ratio unchanged onto early initiators would claim knowledge the trial did not provide.

This limitation is sometimes used too aggressively. "WHIMS started late" is a fair description of its population; "therefore an early start prevents dementia" does not follow. A failed or harmful test in one population can make a timing hypothesis worth testing, but it cannot serve as the positive test of that hypothesis. Nor can a proposed biological explanation retroactively turn an untested age group into a successful trial arm. The first task is to retain both halves of the result: harm when the estrogen-plus-progestin regimen was begun in the tested older population, and uncertainty about whether a substantially earlier start would alter dementia incidence.

Formulation also complicates comparisons. WHIMS tested specific estrogen and, in one trial, progestin regimens; "hormone therapy" covers treatments that are not interchangeable merely because they share a purpose.[5,6] Yet differences between formulations must not become an all-purpose escape clause. When a newer formulation has not been shown to prevent dementia, its difference from an older trial treatment is a reason to avoid overgeneralizing the harm estimate, not a reason to assign it a prevention benefit.

For this book's evidence scale, the WHIMS result earns B harm in the tested older-start population: a controlled human finding with limits tied to whom and what the trial studied. It is not a universal grade of harm for all women at all ages. Its boundary is part of its meaning. That boundary leads directly to the next question: what happened when investigators randomized women much closer to menopause?

Starting Early: KEEPS

KEEPS-Cog tested the idea that starting near menopause might produce a different cognitive result. It randomized 693 women whose mean age was 52.6 and who were, on average, about 1.4 years past their last menstrual period. Participants received one of two hormone regimens, oral conjugated estrogens or transdermal estradiol, each paired with cyclic progesterone, or placebo, and cognition was assessed over four years.[7] This was much closer to the proposed window than WHIMS. It was also a trial of cognitive performance, not a trial designed to determine whether therapy prevented dementia.[7]

Neither hormone regimen produced a cognitive benefit or cognitive harm over the 48-month trial period. The oral conjugated-estrogen group showed some mood benefits, which are not the same endpoint as improved cognition.[7] That separation is easy to lose in casual discussion. Feeling better can matter a great deal to a person living through menopause, but it is not evidence that treatment has postponed Alzheimer's disease. Conversely, the neutral cognitive result is not evidence that treating menopausal symptoms is pointless. The study answered a narrower research question.

A later continuation study looked for a longer-lasting cognitive difference. About ten years after KEEPS ended, investigators invited 622 women to take part; 299 enrolled, and 275 had cognitive data from both phases. Earlier randomization to hormone therapy was not associated with a long-term cognitive benefit or harm compared with placebo.[8] The original treatment assignment gives that comparison more structure than an ordinary survey of past users. Still, participation in the later follow-up was selective, and the continuation cannot be described as though all originally eligible women had remained in a continuously randomized dementia-prevention trial.

Selective follow-up creates a particular interpretive problem. If the women who returned differed in ways relevant to later cognition from those who

did not, the continuation's comparison might not represent the full invited group. That possibility does not make the neutral finding worthless; it limits how much certainty can be extracted from it. The original trial and its continuation point in the same neutral direction for measured cognition, while leaving dementia prevention unproved.[7,8]

The result occupies a useful middle ground. KEEPS is not a replay of WHIMS: its participants began much younger, and it did not find the cognitive harm seen in the older-start dementia trial.[5,7] It is also not proof that the early-start window works. The initial cognitive outcomes were neutral, the later cognitive outcomes were neutral, and neither phase established reduced dementia incidence.[7,8] "Not harmful on these cognitive tests" and "protective against dementia" are different claims, separated by both endpoint and time.

The temptation is to treat a null result as a hidden victory because it did not reproduce WHIMS. But a trial can answer one fear without confirming the opposite hope. If a hypothesis predicted that beginning near menopause would improve later cognitive performance, KEEPS did not demonstrate that improvement. If the concern was that any hormone exposure would necessarily reproduce the older WHIMS finding, KEEPS does not support that sweeping claim either. The practical intellectual gain is a narrower interpretation, not a slogan.

On the series scale, menopausal hormone therapy is B-null for early-start cognitive benefit. Here *B-null* means controlled evidence found no effect on the cognitive endpoint tested; it does not mean every possible treatment, duration, or later dementia outcome has been settled. The grade for the older-start WHIMS harm finding remains separate. Grades attach to claims, not to a molecule's reputation. Combining the two into a single "good" or "bad" score would erase the change in starting age and the change in outcome.

This is where the word *window* needs care. It can mean that effects may differ by the timing of initiation, which is a reasonable proposition to investigate. Or it can be used to imply that a demonstrated prevention interval has already been found. KEEPS supports neither a general replay of older-start harm nor the stronger prevention claim. Its value lies partly in refusing a false choice between those two interpretations.

The Observational Window

The forum's September thread made a different kind of case. It reported an association between hormone therapy and lower all-cause dementia risk in a large postmenopausal cohort, then emphasized women who began treatment within a particular midlife range.[1,2] Large cohorts can reveal patterns that short cognitive trials may miss. They can also bring into view subgroups whose experiences differ. What they cannot do, without further assumptions, is assign treatment as though by lottery.

Consider why someone enters a treatment group in ordinary life. Symptoms, medical history, access to care, preferences, a clinician's assessment, and a woman's age all may bear on that decision. Those same factors may bear on which outcomes are recorded later. Researchers can adjust for measured differences, sometimes extensively, but an adjusted association is still not a randomized assignment. Splitting a cohort into ever more specific subgroups may sharpen a hypothesis while making the apparent precision of a headline more deceptive. A strong-looking estimate in one subgroup need not identify the effect a clinician would produce by initiating treatment in a similar-looking patient.

RapAdmin's second September post called its hazard ratio of 0.90 a "10% relative risk reduction."[2] That wording describes a proportional comparison, not the number of dementia cases avoided. The post did not give the absolute event rates needed to make that translation.[2] A reader who hears "10% lower risk" as "ten out of every hundred women spared dementia" would be assigning an absolute meaning the headline cannot support. This is a problem of communication even before the separate question of whether the association is causal.

The May thread pointed to another possible complication. RapAdmin's summary linked later menopause with some better cognitive trajectories while describing no general cognitive benefit from a history of therapy.[3] The question is not whether that forum account defeats the September account. They concern different analyses and different outcomes. Rather, natural menopause timing could be associated with broader features of health and aging that also relate to cognition. If so, a study that mixes reproductive history, treatment choices, and later brain outcomes faces more than one possible explanation for its results.

A review published in December 2025 offers a broader test of the prevention claim. It included ten studies, one randomized trial and nine observational studies, with a combined 1,016,055 participants. The

certainty of evidence ranged from moderate to very low. Across those studies, menopausal hormone therapy was not significantly associated with incident mild cognitive impairment or dementia. Analyses divided by initiation timing, duration, and therapy type were also nonsignificant.[9] That result does not prove that every possible subgroup effect is exactly zero. It does mean the review did not establish the advertised dementia-prevention window.

A million participants sounds decisive until one asks how the evidence was obtained. Nine of the ten studies in that review were observational.[9] Pooling them does not convert them into nine independent randomized tests of prevention. The overall null result belongs in the lane of a mixed-evidence meta-analysis, with its limits stated plainly. It tempers claims from striking individual cohorts; it does not replace WHIMS or KEEPS as a controlled test of the populations and endpoints those trials actually studied.

Nor does a nonsignificant timing subgroup prove that timing cannot matter. A subgroup analysis may fail to detect a real difference, particularly when studies define exposure and outcomes differently. The narrower conclusion is enough: the review found no significant timing association and therefore did not validate a dementia-prevention window.[9] Keeping that distinction prevents a negative synthesis from being treated as a universal law, while still refusing to turn a favorable cohort headline into an established intervention.

In August 2026, another observational study gave the discussion a more physical endpoint: pathology. Investigators examined self-reported estrogen-only hormone-therapy use in two datasets, including National Alzheimer's Coordinating Center autopsy records for 258 users and 2,701 nonusers, and Alzheimer's Disease Neuroimaging Initiative data for 110 users and 1,948 nonusers. In the autopsy dataset, estrogen-only use was associated with lower odds of increased Alzheimer pathology: an odds ratio of 0.65, with a 95% confidence interval of 0.48 to 0.88. It was also associated with lower odds of clinical dementia diagnoses. The authors cautioned that the retrospective findings did not establish causality and had limited generalizability.[10]

Autopsy evidence adds something a memory questionnaire cannot: a view of tissue pathology after death. It also introduces its own selection problem. People who participate in research programs and whose brains are available for autopsy are not automatically representative of everyone

considering hormone therapy. A report of past estrogen-only use is not a randomized comparison of starting therapy at a specified age. The study can support the question "Why might estrogen-only users in this dataset have shown less pathology?" It cannot answer "Would starting estrogen-only therapy prevent dementia in otherwise similar women?"

Nor should that pathology association be quietly substituted for the overall dementia finding. The 2025 review found no significant association with incident MCI or dementia and no significant initiation-timing subgroup result; the 2026 autopsy analysis reported a favorable estrogen-only association in selected observational datasets.[9,10] Both can be accurately reported because they ask different questions with different designs. A person can have an association with less measured pathology in one research population without a proven treatment effect on dementia incidence in the population a reader has in mind.

There is an additional hazard in the phrase "estrogen-only." The WHIMS estrogen-alone participants had undergone hysterectomy, and their older-start dementia estimate was not statistically significant on its own; the combined WHIMS estimate pointed to harm.[6] The autopsy study's estrogen-only category cannot settle what should be inferred for different treatment histories, different starting ages, or women for whom estrogen-alone therapy is not the relevant comparison. Similar words on a chart do not make study populations exchangeable.

The observational window remains a research question, not a prevention service already on offer. Timing may modify an effect. Timing may also identify differences in who received treatment and when. The distinction is not semantic: a prevention claim asks what happens because therapy is started, whereas an observational association describes what happened among people whose histories already differed. Published evidence has not bridged that gap to show that choosing an early start prevents dementia.[7,8,9]

What the Label Change Did Not Show

In February 2026, the US Food and Drug Administration approved labeling changes for six menopausal hormone-therapy products. Statements about cardiovascular disease, breast cancer, and probable dementia were removed from boxed warnings. The products covered several categories, including systemic combination and estrogen-alone therapies and topical vaginal estrogen.[11] A contemporaneous report described the action as the first approved labeling revisions following the agency's November 2025 request.[12]

As of October 2026, that is a regulatory status fact, not a newly completed randomized dementia-prevention trial.[11] A boxed warning is part of product labeling; changing its placement or content is an agency judgment about how risks should be communicated across the products concerned. It does not by itself produce a new estimate of what happens to dementia incidence when a woman begins therapy near menopause. The randomized evidence discussed here remains WHIMS for older initiation and KEEPS-Cog for cognitive outcomes after initiation near menopause.[5,6,7]

The distinction can feel unsatisfying. A reader might reasonably ask how a warning could change while a trial's historical result remains true. But regulatory communication and scientific inference are not identical operations. The WHIMS estrogen-plus-progestin result still describes increased probable dementia in its tested older population.[5] KEEPS-Cog still reports no cognitive benefit or harm over its four-year early-start trial, with a neutral later follow-up.[7,8] The label action does not require either study to disappear, and neither study alone dictates every word on every current product label.

For anyone encountering a confident claim that "the FDA removed the dementia warning," the missing second sentence matters. The FDA approved removal of probable-dementia language from boxed warnings for the six products; it did not announce that hormone therapy prevents dementia.[11] The former is verifiable regulatory news. The latter would require efficacy evidence directed at prevention. Conflating the two turns a change in risk communication into an invented clinical result.

This separation also protects a legitimate discussion of menopausal care from being made to carry an unsupported Alzheimer's claim. Hormone therapy has indications and risks that belong within its product labeling and a clinical assessment of menopausal concerns. Dementia prevention is not an established reason to prescribe it.[9,11] People can debate how labels

should convey age, formulation, and indication without claiming a cognitive benefit that the early randomized test did not find.

For the broader method of weighing a striking headline against the design of the study beneath it, see *The Longevity Operating System*, Chapter 2, "The Hierarchy of Evidence." The discipline here is modest but firm: a regulatory reassessment can change what a box says; it cannot turn an observational timing hypothesis into demonstrated prevention.

The Men's Evidence

The men's hormone discussion has a different starting point but a familiar vulnerability to endpoint confusion. Testosterone may be discussed alongside energy, mood, body composition, and memory, as if improvement in one domain would establish improvement in another. The controlled memory test should come first. In the cognitive arm of the Testosterone Trials, 493 men with low testosterone and age-associated memory impairment, whose mean age was 72, were randomized to testosterone gel or placebo for one year. The primary delayed-paragraph-recall comparison showed no difference: an estimated difference of −0.07, with a 95% confidence interval from −0.92 to 0.79. Visual memory, executive function, and spatial ability were also not improved.[13]

That is a direct test of a cognitive claim in a relevant older group, though not a trial of dementia incidence. Its null result should not be inflated into a statement about every symptom associated with low testosterone. Equally, evidence concerning other symptoms should not be moved into the memory column. The trial asked whether treatment improved measured cognitive performance in men selected partly for memory concerns, and it did not find that benefit.[13]

TRAVERSE is often invoked because it randomized far more men: 5,204 with hypogonadism received testosterone or placebo in the parent trial. Its prespecified HIS-Q substudy assessed mood, energy, sleep, and a self-reported cognition domain. Testosterone modestly improved mood and energy, but not self-reported cognition or sleep.[14] That cognition domain was a report of perceived symptoms, not a dedicated battery of neuropsychological memory tests. TRAVERSE had no dedicated cognitive substudy; calling HIS-Q one would misidentify what investigators measured.[14]

This correction matters even though both results point away from a demonstrated cognitive benefit. The T Trials provide the randomized memory-test result; TRAVERSE contributes an unchanged self-reported cognition domain from a much larger trial.[13,14] Two neutral observations are not made stronger by mislabeling one of them. If anything, precision makes the conclusion more credible: the formal cognitive test was null, and the large trial's symptom measure did not suggest an overlooked improvement in perceived cognition.

A 2025 meta-analysis of 14 studies of androgen replacement in hypogonadal men reported a positive pooled overall cognition estimate, a standardized mean difference of 0.454, with positive pooled estimates for memory and executive function. Its authors also detected publication bias.[15] The favorable number deserves mention, not automatic adoption. When a small, heterogeneous collection of studies may preferentially contain positive published results, its pooled estimate can overstate a benefit. That limitation is especially relevant beside the null randomized T Trials memory result.[13,15]

The disagreement is more informative than a vote count between positive and neutral papers. A pooled standardized effect summarizes results across differing studies; it does not say how many men would avoid dementia, or even establish that dementia was the outcome tested.[15] The T Trials asked a more direct memory question in older men with complaints and found no measured gain.[13] TRAVERSE's much larger enrollment adds context, but its cognition measure was self-reported.[14] Each result belongs beside its actual endpoint.

The studies cannot be made identical. They enrolled different people and assessed cognition in different ways. A positive pooled estimate may generate questions about which outcomes or populations deserve another careful test. It does not overturn a larger, direct null test by force of arithmetic alone, and it does not justify prescribing testosterone for cognition. The T Trials did not establish memory benefit in the older men they studied; TRAVERSE's self-reported cognition domain was unchanged.[13,14]

The series grade for testosterone in men is B-null for the tested cognitive claim, based on the T Trials: controlled human evidence found no improvement on the measured cognitive endpoints. TRAVERSE HIS-Q is supporting context, not a cognitive substudy.[13,14] This grade does not deny that testosterone may have uses within its approved labeling for diagnosed

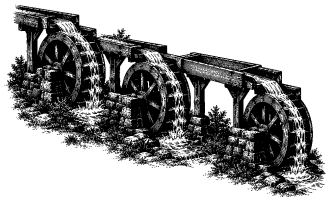
hypogonadism. It says the evidence presented here does not support prescribing it to prevent dementia or improve cognition.

For hormone and body-composition claims without repeating prescribing material, see *The Metabolic Frontier*, Chapter 14, "Supplements, Body-Composition Drugs, and Peptide Stacks."

Across women's and men's studies, the restraint is the same even though the evidence is not. WHIMS found increased probable dementia when one hormone regimen was begun in women 65 and older; KEEPS found no cognitive gain when therapy began much nearer menopause; the T Trials found no measured cognitive gain from testosterone in older men with low testosterone and memory concerns.[5,7,13] Observational findings may help explain why these questions persist, but timing alone cannot manufacture the missing prevention result. The window remains a hypothesis to test, not a reason to promise protection.

Part IV: The Forum's Pharmacy

Chapter 12: Refueling the Cell: NAD+, GlyNAC, and Creatine



On January 13, 2024, a forum member named Alex put a question to the group: “which is the most efficacious in raising NAD+?” Alex was comparing nicotinamide mononucleotide, or NMN, with nicotinamide riboside, or NR. The question was about a laboratory value, not memory. But in a community worried about aging brains, the next step was easy to imagine: if either compound raised NAD+, might it restore something a person was losing?[1]

That is the hinge on which much of the cell-refueling market turns. A blood measurement goes up. A mechanism sounds favorable. A person hopes to feel clearer, remember a conversation, or remain independent longer. Each link may be plausible without making the whole chain true. This chapter follows three candidates. NAD+ precursors, GlyNAC, and creatine, through the same question: did a changed marker become a changed life?

The distinction matters to the forum’s people because their interest is not abstract. A laboratory result can offer relief from uncertainty, especially when there is no simple test of whether an apparently healthy person will develop Alzheimer’s disease. Yet a marker is useful for this purpose only if changing it reliably changes an outcome people care about. A trial can establish that a compound entered the bloodstream and affected a pathway while leaving memory, daily function, and dementia risk unresolved.

The Broken NAD+ Chain

NAD+, short for nicotinamide adenine dinucleotide, helps cells carry out reactions involved in energy metabolism. NR and NMN are presented as precursors: materials the body can use in making NAD+. That biological relationship makes the pitch unusually tidy. Instead of asking people to accept an obscure claim about "brain vitality," a seller can point to a molecule with an established cellular role and a value that can be measured.

The trouble begins when three different propositions are treated as one. The first is that an intervention changes NAD+ or related compounds in blood. The second is that it changes the relevant biology in the brain. The third is that it preserves cognition or prevents dementia. Evidence for the first does not automatically establish the second, and neither establishes the third. Blood is accessible; brain tissue is not. Even a demonstrated change inside the brain would still leave open whether it helped a person think or function.

Alex's question captured the first proposition cleanly. In the same discussion, Neo described before-and-after testing by someone else; the post conveyed interest in measuring a response, not evidence of a cognitive outcome.[2] The distance between a personal measurement and a clinical result is precisely where expectation, ordinary variation, and selective attention can exert their influence. Someone may notice a good week after seeing a favorable number and remember it longer than an ordinary week that followed the same result.

The forum was not of one mind about the earlier NMN literature. In April 2022, MAC called a reported biological-age result "essentially meaningless" and raised concerns about the reproducibility of early DNA-age tests.[3] Two days later, EnrQay questioned whether participants had truly remained unaware of their assignments and pointed to differences between groups and manufacturer sponsorship.[4] These were members assessing a particular study, not findings established by the trials examined in this chapter. Their questions nevertheless show why an eye-catching percentage deserves scrutiny before it is carried into a claim about an aging brain.

A later forum thread gave the broader problem a sharper title: "NAD+ Precursors Hit a Clinical Wall: Biomarker Success But Functional Ambiguity." RapAdmin argued there that circulating changes did not consistently become measurable functional benefits. That was a member's reading of a research review, not a clinical trial conducted by the forum; its

value here is that it shows the community questioning its own favored markers.[5] Skepticism did not end the underlying hope. If a person notices more energy during a self-experiment, the experience may be real to that person while remaining unable to identify what caused it, or whether anything relevant to Alzheimer's disease has changed.

A six-month randomized pilot published in June 2026 illustrates both the attraction of a mechanistic result and the limits of interpreting it. Thirty participants with mild cognitive impairment were assigned to a supplement combining a ketone compound with NR or to placebo, with 15 in each group. PET-measured gray-matter ketone uptake increased 2.4-fold in the active group, and white-matter uptake increased 3.1- to 3.6-fold across seven tracts. In parts of the fornix, a white-matter structure involved in memory circuits, myelin-density decline appeared in the placebo group but not the active group. Changes in processing speed were associated with the imaging measures.[6]

These are interesting observations, not proof that NR rescued memory. The intervention contained both ketones and NR, so the design cannot isolate NR's contribution. The sample was small, and an association between processing speed and an imaging measure does not by itself establish that one caused the other. The PET result measured ketone uptake, not a demonstrated rise in brain NAD+; the study did not establish that the combined intervention prevented dementia.[6] It gives researchers a reason to ask more specific questions, including which component might matter and whether the measured changes persist alongside meaningful clinical gains.

The trial also illustrates a common interpretive trap in combination studies. If two ingredients are introduced together and an outcome changes, neither ingredient can claim the full result on its own. Nor does the result establish that the pair is better than either component separately. Those distinctions may sound technical, but they determine whether a reader learns something about NR or about one particular combined intervention.

For NR and NMN, the evidence-grade headline is Insufficient for preventing dementia or slowing cognitive decline in at-risk adults without dementia. The series also assigns B-null to cognition endpoints tested in small controlled trials: a controlled negative result on those particular measures, not a proof that every possible use or population has been exhausted. The blood-marker lane is stronger than the prevention claim,

but a biochemical response cannot fill in missing clinical outcomes. The distinction keeps an unfavorable trial from being dismissed merely because a compound demonstrably does something in the body.

There is a subtler failure mode here. Researchers may select a population in whom a pathway seems especially relevant, confirm target engagement, and still find no useful effect on function. That does not show the pathway was imaginary. It may mean the intervention changed too little in the relevant tissue, changed the wrong part of a larger network, or addressed a process that was not limiting the person's performance. A mechanism can be sound and a treatment ineffective at the same time.

A Regulatory Reversal and a Clinical Null

NMN acquired a separate story in the United States: what could legally be sold as a dietary supplement. In a response dated September 29, 2025, the Food and Drug Administration concluded that NMN was not excluded from the dietary-supplement definition under the drug-preclusion provision it had been asked to address. The agency cited evidence of NMN marketing as a U.S. Supplement as early as 2017, before authorization for its investigation as a new drug. A trade-publication account described the change in the agency's application of the race-to-market rule.[7,8]

A September 2025 forum exchange caught the uncertainty before that answer arrived. Steve_Combi wrote, "Decision has been delayed until Sept 30, we'll see."[9] The subsequent FDA response resolved the particular classification question it addressed. It did not resolve the question that opened this chapter: whether changing an NAD+ measure preserves memory.[7]

As of October 2026, the practical regulatory point is narrow: FDA no longer considers NMN excluded from the dietary-supplement definition under the drug-preclusion provision addressed in its petition response. That is not approval of an NMN product as an Alzheimer's treatment. The response does not establish cognitive efficacy or remove other applicable safety and regulatory requirements.[7] A legal classification answers a question about a statute. It does not answer whether a person remembers better after using the product.

The separation can be hard to maintain when a once-disputed product appears under a favorable headline. A reader might reasonably infer that an agency has reviewed the evidence and changed its mind about the

product's benefits. That is not what the petition response says.[7] The relevant evidence for cognition must still come from studies measuring cognition, function, or disease outcomes, with designs capable of distinguishing an effect from chance and expectation. The regulatory event changed the argument about classification; it did not repair the broken NAD+-to-memory chain.

Another October 2026 result put functional outcomes in the foreground. In NOPARK, a randomized trial published on October 8, 410 people with early Parkinson disease were assigned to NR or placebo for 52 weeks; 393 were included in the primary analysis. On the trial's combined measure of Parkinson-related experiences and motor signs, scores worsened more in the NR group. The adjusted between-group difference was 2.72 points, with a 95% confidence interval from 0.47 to 4.98, favoring placebo. The authors concluded that the findings did not support NR as a disease-modifying Parkinson treatment.[10]

A University of Bergen account of the trial also reported no imaging benefit and similar adverse-event rates in the two groups.[11] NOPARK is a useful correction to the habit of treating a promising mechanism as sufficient. It followed a controlled comparison for a year and asked about clinical performance, not simply whether a molecule could be raised. On the tested clinical measure, the result favored placebo.[10] Similar adverse-event rates do not turn that finding into a benefit; they address a different question.[10,11]

The difference between groups also needs its proper scale. The reported 2.72 points are an adjusted difference on a Parkinson-specific score, not a percentage reduction in dementia risk and not a count of people who retained independence. Its confidence interval indicates uncertainty about the size of the difference, even as the reported interval favors placebo.[10] Translating a score difference into a claim about Alzheimer's prevention would cross both an outcome boundary and a disease boundary.

Parkinson disease is not Alzheimer's disease. NOPARK was not a dementia-prevention trial, and its participants cannot stand in for adults without cognitive symptoms.[10] Its proper force is more disciplined: a biologically appealing NAD+ precursor failed to improve a meaningful controlled outcome in a neurodegenerative condition. That raises the standard of proof for claims that changing NAD+ will necessarily protect the brain, while leaving the Alzheimer-specific question unanswered. Calling it proof that NR can never help any brain disorder would overreach just as surely as calling a blood change proof that it can.

The result also clarifies why duration and population matter. A brief study may show a biochemical effect before it could plausibly detect a durable difference in function. A year-long study in people with an established disease poses a harder clinical test, but of a different claim from prevention before symptoms. Neither kind of trial should be made to answer a question it was not built to ask. The responsible comparison is between a claim and the population, intervention, comparator, and outcome actually tested.

For readers of a prevention book, the conclusion remains unsatisfying in an honest way. NOPARK found no functional benefit from NR in early Parkinson disease.[10] Small cognition trials offer narrower negative evidence. Neither establishes the effect of NR or NMN on future Alzheimer's incidence in otherwise healthy adults.[10,11] The Insufficient headline therefore remains in place even though some specific tested endpoints have earned B-null. Those grades describe different claims, not a contradiction.

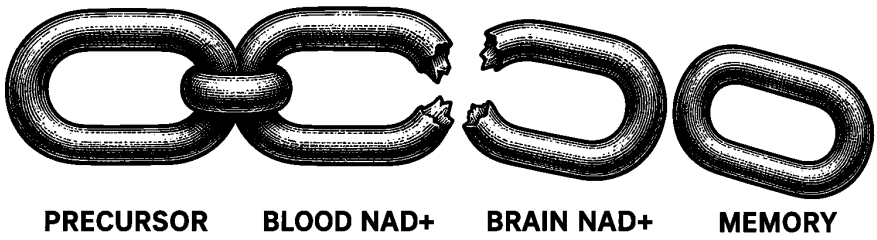


Figure 10. The NAD+ chain. Precursors such as nicotinamide riboside (NR) and NMN raise NAD+ in blood. Evidence that they raise it in the human brain is limited, and no trial has shown a memory or dementia benefit. In NOPARK (410 people with early Parkinson's disease, 52 weeks), NR gave no clinical benefit.

The figure's missing arrow is the point: raising a circulating marker, reaching the brain, changing brain biology, and preserving daily ability are

separate steps. A study may observe one step cleanly and still leave the next untested. Treating the arrows as automatic is how a plausible hypothesis becomes an unearned promise.

GlyNAC Before Its Alzheimer Trial

GlyNAC brings the same question into a different pathway. It combines glycine with N-acetylcysteine, or NAC, as building materials for glutathione, a compound involved in cellular defenses against oxidative stress. The appeal is easy to hear: if aging cells appear stressed, why not replenish a component of their protective machinery? But "more glutathione" and "less Alzheimer's disease" are distinct findings. The second cannot be inferred simply by measuring the first.

The forum's GlyNAC conversation became large and persistent. A thread begun in May 2022 ran to hundreds of posts in the refreshed archive, mixing interest in mechanisms with reports of individual experiments and disagreements about what animal findings meant.[12,13] Its size documents sustained curiosity, not a second clinical evidence stream. People who choose to report experiences are not randomly assigned; other health changes can occur at the same time, and the absence of a reported problem cannot establish safety or cognitive benefit. Warmth toward their effort does not require treating the discussion as a substitute for a comparison group.

For the fuller account of supplements, GlyNAC, and the forum effect, see Book One, *The Longevity Operating System*, Chapter 13.

The Baylor group reported its older-adult GlyNAC findings in a December 2024 conference abstract. It describes effects in older adults, including a cognitive signal, but it is abstract-level evidence, not a full peer-reviewed paper reporting cognitive results.[14] An abstract can announce a signal and help justify another study. It offers less opportunity to inspect missing data, outcome selection, and the size and consistency of effects than a complete report.

A larger project may improve that situation, but a funding record is not a completed replication. A February 2026 NIH record describes a planned randomized GlyNAC study in 150 older adults, comparing two study groups over 24 weeks and including measures of glutathione, oxidative stress, mitochondrial function, physical function, and quality of life. Its listed performance period extends to January 2031. It does not provide

completed outcomes and is not itself an Alzheimer's trial result.[15] The number of intended participants makes the next test more substantial than a small pilot, but plans do not earn an outcome grade.

The directly relevant registered study is NCT04740580. It compares GlyNAC with an alanine placebo in people with Alzheimer's disease, with estimated enrollment of 52 and planned measures spanning cognition, glutathione, brain glucose uptake, inflammation, and other metabolic outcomes. At its September 3, 2026 update, the registry listed it as active, not recruiting, and posted no results.[16] As of October 2026, its readout must not be described as favorable, unfavorable, or complete on the basis of that record. The trial is where the promising pathway meets an Alzheimer-specific controlled test; until results are available, the answer remains pending.[16]

A registry creates another easy misunderstanding. "Active, not recruiting" describes a study's administrative status, not its success, and an estimated enrollment is not a reported analysis population.[16] It would be possible for a finished report to differ from the plan in ways that matter to interpretation. Until there is a result to examine, the listed outcomes identify what investigators intended to measure; they cannot tell us which measures changed.

Even a favorable glutathione result from that study would leave a further question. If the active group's marker changes but its cognitive measures do not, the experiment would support target engagement without demonstrating a benefit a patient could use. If cognition appears to improve, the trial's size, prespecified analyses, and consistency across outcomes will matter. This is not a demand for perfection before learning anything. It is a way to avoid promoting whichever measure happens to move while overlooking the one that motivated the study.

NAC alone is sometimes drawn into the GlyNAC argument, although the interventions are not interchangeable. A 2026 systematic review covering 23 studies across seven neurological disorders included five Alzheimer's disease studies. It found that Alzheimer-related signals came in part from formulations containing NAC alongside other active ingredients. Those designs cannot identify NAC's independent contribution, and the review judged most included studies to have high or serious risk of bias.[17] A mixture that appears promising cannot tell us which ingredient, if any, did the work.

A controlled result in another population provides a useful boundary rather than a verdict on GlyNAC. In a 24-week trial, 59 adults with possible vascular mild cognitive impairment received NAC or placebo alongside exercise-based cardiac rehabilitation. Executive function improved over time in both groups, but the between-group difference was not significant: NAC added no demonstrated cognitive benefit in that comparison. The study tested NAC, not GlyNAC, and possible vascular MCI, not Alzheimer's disease.[18] Its null result should neither be hidden nor made to answer the wrong question.

The rehabilitation context matters. If both groups improve while the difference between them remains uncertain, reporting only the before-and-after improvement in the NAC group would wrongly assign a shared change to the supplement. The placebo group shows what happened over the same period without NAC added to rehabilitation.[18] That is why a comparison can overturn a persuasive account of improvement without denying that participants improved.

The headline grade for GlyNAC is Insufficient pending the Alzheimer trial. No completed study has shown that it prevents dementia or slows cognitive decline in at-risk adults without dementia. The older-adult abstract, the planned larger trial, and the active Alzheimer registry each occupy a different rung: preliminary report, research commitment, and unfinished controlled test.[14,15,16] Listing them together can make the evidence look larger than it is unless their stages remain visible.

This is also a case in which an apparently modest intervention can attract an outsized conclusion. Glycine and NAC sound familiar compared with an experimental drug, and a favorable antioxidant marker sounds reassuring. Familiarity does not settle long-term outcomes or make an Alzheimer claim less demanding. The stakes of the claim, not the exotic quality of the ingredients, set the evidentiary bar.

Creatine's Small Human Foothold

Creatine enters the chapter with a different practical reputation. Many readers know it from muscle and exercise discussions, where the idea of cellular energy has a more concrete home than it does in dementia prevention. The brain also has energy demands, and that makes the possibility of changing brain creatine worth investigating. But a plausible need for energy is not evidence that adding a particular supplement preserves cognition.

The CABA pilot made a particularly useful first measurement: not only whether participants could remain in a study, but whether brain creatine changed. Published in May 2025, it enrolled 20 adults with Alzheimer's disease whose mean age was 73.1 years. The study was single-arm and open-label, not a randomized controlled trial. Nineteen participants met its adherence threshold. Brain total creatine rose by 11%, and global and fluid cognition composites improved from baseline.[19]

The brain measurement answers a question that blood NAD+ alone cannot answer for NR and NMN. In this pilot, an intervention was associated with a measurable change in the organ of interest.[19] That is a genuine advance in specifying the hypothesis. It does not, however, provide the missing comparison. Without a placebo group tested over the same period, the cognitive improvements cannot be confidently assigned to creatine. Practice with repeated tests, ordinary variation, changes in care, and participants' or researchers' expectations remain possible explanations.

There is also an absolute-versus-relative distinction hiding in the 11% figure. It describes the change in measured brain total creatine, not an 11% improvement in memory or an 11% reduction in Alzheimer's progression.[19] Attaching the percentage to the wrong outcome would turn a mechanistic observation into an efficacy claim. The improved cognition composites deserve attention too, but because everyone in the pilot received the intervention, their change has no untreated reference group.[19]

Feasibility is another legitimate outcome with a different meaning from efficacy. If participants cannot stay with a protocol or investigators cannot collect usable brain measurements, a larger trial may be impractical. CABA showed that 19 of its 20 participants met the study's adherence threshold and that brain creatine could be measured as an outcome.[19] Those observations help design the next experiment. They do not show that the intervention slowed the disease.

The pilot also took place in adults already diagnosed with Alzheimer's disease.[19] A trial in symptomatic disease could eventually test whether creatine affects cognitive change there. It would still not automatically establish prevention in adults without dementia. The two questions differ in the condition of the brain at entry, the time available for a benefit to appear, and the outcomes that can be observed. Stretching a finding across both populations would repeat the same error seen with NAD+.

The series grade for creatine is C: uncontrolled human evidence for the brain-related claim, rather than a controlled demonstration of cognitive

benefit. CABA's 11% brain-creatine rise is a biomarker finding, and its cognition changes are observations within the same unblinded group.[19] Calling the pilot worthless would miss what it accomplished. Calling its before-and-after cognition result proof of treatment would miss what its design cannot do.

That middle position is harder to sell than either excitement or dismissal. The study made the proposed mechanism more testable by showing a brain measurement could move. The proper follow-up question is whether people assigned to creatine fare differently from people assigned to a credible control, under conditions that reduce expectation and account for repeated testing. The pilot gives researchers a foothold, not a finished staircase.

The Clinic Market Is Not a Trial

NAD+ has also been sold in settings that make the intervention feel more medical than a bottle on a shelf. The appearance of clinical supervision, a measured value, or a premium service can imply that efficacy has already been settled elsewhere. It has not. No controlled study has shown that NAD+ IV infusions improve cognition or treat neurodegenerative disease. The grade for NAD+ IV infusions is Insufficient/E: insufficient clinical outcome evidence, with E denoting testimony or hypothesis rather than a controlled result.[20]

The safety record should be read with equal care. In a warning letter dated January 20, 2026, FDA said an inspected outsourcing facility had compounded NAD+ products using a bulk substance ineligible for the section 503B exemptions at issue. The letter also described reports of low blood pressure, uncontrollable shaking, chills, and body aches associated with an NAD+-containing product.[20] That is a serious regulatory and adverse-event signal. It is a company-specific letter, however, not a measured rate of harm for every product in the category and not a blanket prohibition on all NAD+ infusions.[20]

Neither extreme reading helps. The letter should not be used to claim that every person exposed to such a product will have those symptoms. Nor should its limited scope be used to wave away the reported events or the facility problem FDA identified.[20] Product quality is a separate uncertainty from biological efficacy: a perfectly characterized product could still fail to help memory, while a poorly controlled one could add risks before its supposed benefit has been demonstrated.

For the broader discussion of gray-market supply-chain risks, see Book Four, *The Metabolic Frontier*, Chapter 18.

The contrast between a clinic service and a trial can be stated plainly. A trial defines who entered, what comparison was made, what outcomes were measured, and how unfavorable results will count. A clinic may collect testimonials from people who return and hear little from those who did not improve. That difference is not an accusation about every practitioner or every patient's experience. It explains why a room full of sincerely reported improvement cannot supply the missing denominator or control group.

Across the three evidence stories, the markers grow more intimate: NAD+-related measures in blood, ketone uptake on a brain scan, glutathione-related measures, creatine inside the brain itself.[6,14,19] Each can make a hypothesis more precise. None is identical to remembering a route home, following a conversation, or retaining the capacity to manage ordinary life. The further a claim travels from a measured marker toward those outcomes, the more carefully its supporting study must bridge the distance.

The forum often saw that gap before a marketing page would admit it. Members compared laboratory values, challenged study design, and returned to what they themselves felt.[1,4,5] Their posts are a record of people trying to make sense of uncertainty, not a replacement for randomized evidence. The humane response is neither to ridicule a felt improvement nor to promote it as prevention. It is to keep the person, the marker, and the trial outcome distinct.

Status as of October 2026

As of October 10, 2026, FDA's September 2025 petition response says NMN is not excluded from the dietary-supplement definition under the provision it addressed; NOPARK's October 8 publication reports no clinical benefit of NR in early Parkinson disease; and FDA's January 2026 NAD+ warning letter documents facility concerns and adverse-event reports. These dated primary records should be checked for subsequent changes or corrections.[7,10,20]

As of October 10, 2026, the GlyNAC Alzheimer trial's September 3 registry record lists it as active, not recruiting, with no results posted. Its registry status and any later readout should be verified against the current record before treating the trial as evidence of an outcome.[16]

Chapter 13: Peptides in the Gray Zone



On February 1, 2024, ksbradley opened a forum thread called “Peptides / Bioregulators.” Members described self-experiments with several peptides.[1] By October 9, 2026, the thread held 1,157 posts.[1] That is an immense archive of curiosity, but its size is not a clinical-trial result.

The appeal is understandable. A peptide can sound more precise than a supplement: a defined sequence of amino acids, a proposed cellular target, perhaps a paper describing an effect in an injured animal. Forum members compared impressions, questioned claims, and sometimes changed their minds in public. Those exchanges can be useful records of what people hope to achieve and what worries them. They cannot establish that an intervention protects a brain over years, especially when the products, outcomes, and people reporting them differ.

This chapter is about a set of refusals. Availability is not evidence of benefit. A stroke-rehabilitation finding is not a dementia-prevention finding. An animal experiment is not a human cognitive outcome. And a vote about what pharmacists might someday be permitted to compound is neither a drug approval nor a finding that a substance works. Keeping those boundaries intact is less exciting than a new protocol. It is also the only way to tell what has actually been learned.

A Thread Larger Than the Evidence

The first distinction is between a community's record and a research record. The forum thread gathered firsthand accounts and questions across more than two years.[1] A member's report can identify a concern worth investigating; several reports can reveal a recurring question. Neither has the safeguards that make a controlled comparison interpretable: a specified population, consistent products, prespecified outcomes, and a way to count people who saw no benefit or never returned to report one.

DeStrider captured the information problem on February 2, 2024: "I'm interested in peptides but haven't taken any action because my knowledge of them is limited. Is there a peptide primer available?"[2] That question deserves a better answer than a catalog of purported effects. "Peptide" describes a kind of molecule, not a common evidence grade. A clinically established peptide drug, an investigational compound, and a product with uncertain identity cannot be treated as interchangeable merely because all contain amino-acid chains.

There was skepticism alongside interest. On December 27, 2025, RapAdmin wrote, "I hope more research comes with it on their efficacy and risks."[3] It is a modest wish, and a useful corrective to the idea that a forum discussion must divide neatly into believers and opponents. People can be interested in an intervention while recognizing that its effects and hazards remain poorly measured.

The thread also shows how readily distinct aims can merge. Someone interested in recovery from an injury may be talking beside someone interested in workouts, aging biology, or memory. Even if one account were perfectly accurate, an improvement in a joint or a perceived change in energy would not settle a claim about Alzheimer's disease. The proposed benefit has to be stated before the evidence can be graded. Here the headline claim is preventing dementia or slowing cognitive decline in adults at risk who do not have dementia.

There is a counting problem as well. A vivid improvement is likely to attract attention; an uneventful experience may never become a post. A thread does not reveal how many people considered an experiment and declined it, how many felt no change, or how many stopped participating. These gaps do not make members dishonest. They make the archive unsuitable as a denominator for estimating benefits or harms.

Semax and Selank illustrate the gap between a recognizable name and a well-tested claim. A Russian-language Semax report followed 110 people after ischemic stroke for five months. Rehabilitation began at a mean of about 89 days after stroke in an earlier group and 214 days in a later group. The report described randomized subgroups receiving or not receiving Semax and reported better recovery on measures including the Barthel Index, as well as changes in plasma BDNF.[4] The published report leaves substantial questions about study quality, and the patients were undergoing post-stroke rehabilitation, not participating in a dementia-prevention study.[4] BDNF is biologically interesting, but a change in its plasma level does not show that fewer people will develop dementia.[4]

The different starting points matter. Someone entering rehabilitation roughly three months after a stroke may face a different recovery course from someone entering roughly seven months after it.[4] That does not invalidate the report's subgroup comparison. It does mean that its design and analysis deserve close inspection before a recovery difference is attributed confidently to Semax. Even a carefully conducted comparison would still answer a post-stroke question rather than the prevention question posed here.

A 2020 Alzheimer's Drug Discovery Foundation evidence review found little evidence that Semax improves cognition in healthy people and no evidence for Alzheimer's disease. It also described the published human literature and safety information as limited.[5] The sources assembled for this chapter contain no Selank-specific human efficacy study on which to base a dementia-prevention claim. That absence is not proof that Selank cannot work. It means a positive claim cannot be supported here by the kind of human outcome evidence the claim requires.

The grade for Semax and Selank is Insufficient for dementia prevention. "Insufficient" does not mean that the forum has failed to generate enough enthusiasm, nor does it erase a narrower post-stroke report. It means that no published human result demonstrates prevention. Even a convincing result in stroke recovery would leave open whether the same intervention changes cognition years later in people who have not had a stroke.

There is a further reason to resist a shortcut from mechanism to prevention. A molecule might affect a process associated with brain injury yet fail to alter the clinical outcome readers care about. Conversely, a measured signal may change without revealing which of several processes produced it. The Semax BDNF finding and rehabilitation scores can

generate hypotheses, but they cannot answer a question they were not designed to test.[4]

That distinction is not hostility toward international research. Studies do not become worthless because they were conducted or published outside the United States. Their methods, comparators, endpoints, and reporting still need the same scrutiny applied to any other study. Nor does skepticism about a peptide imply that all dementia-prevention evidence is equally thin. Different claims stand or fall on different populations and outcomes; the standard does not become looser because a proposed mechanism sounds plausible.

For how peptide-stack claims are assessed, see *The Metabolic Frontier*, Chapter 14.

Stroke Data Are Not Prevention Data

Cerebrolysin offers a particularly tempting substitution of one outcome for another. The CARS trial was a randomized, placebo-controlled, double-blind study of people in early post-stroke rehabilitation. Both groups received a standardized rehabilitation program; the primary outcome was arm function on the Action Research Arm Test at day 90. The reported Mann–Whitney estimator was 0.71, with a 95 percent confidence interval of 0.63 to 0.79, in favor of Cerebrolysin. The investigators described the trial as relatively small and exploratory and called for confirmation in a larger randomized study.[6]

The estimator deserves a moment of care. It is not a statement that 71 percent of treated patients recovered, or that an individual patient gained 71 percent more arm function.[6] Without the underlying absolute scores in view, turning 0.71 into a plain-language claim about the size of a patient's improvement would overstate what this summary can support. The confidence interval reports uncertainty around the trial's comparative estimate; it does not answer whether the improvement would persist, matter equally across patients, or appear in another setting.[6]

CARS is more informative than an animal experiment or a forum account. It has a comparison group and a defined functional outcome in humans. It is also evidence about a specific question: whether an intervention added to rehabilitation improved an arm-function measure after stroke. Stroke recovery is not interchangeable with preventing Alzheimer's disease. The

patients' starting condition, the treatment setting, the time horizon, and the outcome all differ from those in a prevention claim.

The other side of the stroke record matters, too. A 2023 Cochrane review included seven randomized trials involving 1,773 participants with acute ischemic stroke. Across six studies with 1,689 participants, adding Cerebrolysin or a similar agent probably did not reduce all-cause mortality. The reviewers judged there to be moderate-certainty evidence of no benefit for preventing death and noted a possible increase in non-fatal serious adverse events with Cerebrolysin. They also identified limitations, including the small number of studies and manufacturer involvement in three trials.[7]

CARS and Cochrane need not be forced into a false contest in which one "wins." Arm function after rehabilitation and death after acute stroke are different endpoints. An intervention might improve one without changing the other. The Cochrane safety signal, meanwhile, is relevant to any attempt to portray the stroke literature as a simple story of benefit. Neither finding demonstrates that Cerebrolysin prevents dementia in people without symptoms.[6,7]

The numbers in the review can also mislead if stripped of their outcomes. Seven trials and 1,773 participants sound substantial beside a single exploratory trial, but the mortality finding draws on six studies and 1,689 participants, not on a pooled test of dementia prevention.[7] More participants can improve confidence in an answer to the question actually measured. They cannot supply an outcome that investigators did not collect.

Cerebrolysin is Insufficient for dementia prevention on the series scale. Its narrower human stroke evidence does not vanish; it stays in the stroke lane. That is what a claim-specific grade is for. A person who sees "human randomized trial" in a description might reasonably expect a stronger answer than "Insufficient," until the endpoint is named. The trial tested arm recovery. The headline claim concerns future cognitive decline. They are not the same experiment.

There is a practical interpretive trap in rehabilitation research. Recovery after a major event is uneven, and the support a patient receives alongside a study treatment can be substantial. CARS used a standardized rehabilitation program in both groups, which helps make its comparison meaningful.[6] It does not make rehabilitation an invisible detail or turn a

post-stroke result into a general brain-maintenance result. The setting is part of what was tested.

The mortality review poses a different challenge to promotional summaries. “No mortality benefit” does not by itself refute a particular functional score, just as a favorable functional score cannot cancel a possible increase in non-fatal serious adverse events.[6,7] A fair account keeps both findings visible and resists combining them into a single verdict on a much broader cognitive claim. If a dementia-prevention study were eventually conducted, it would require its own population, outcomes, and safety assessment.

Regulatory shorthand can distort the picture as well. FDA Import Alert 66-41 describes a general mechanism for detention without physical examination of identified unapproved new drugs from firms on an alert’s Red List. Its page does not specifically identify Semax, Selank, or Cerebrolysin, so it should not be cited as proof about a particular one of those substances, shipments, or sellers.[8] The general point remains narrower and firmer: an unapproved new drug has not gone through FDA review establishing its safety and effectiveness for the claimed use.[8]

A trial result can be promising without being decisive; a review can be cautious without declaring every earlier observation false. Those are ordinary features of evidence, not signs that one side is hiding the answer. In this case, the conspicuous unanswered question is prevention. Published studies of Semax and Cerebrolysin concern stroke; no published study has shown that either compound, or Selank, prevents dementia.[4,5,6,7]

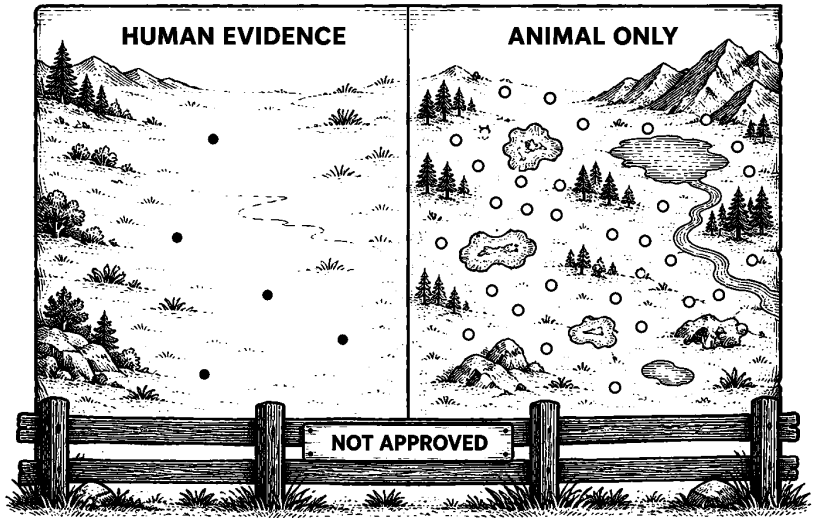


Figure 11. The peptide evidence map. Semax and cerebrolysin have human stroke data but no dementia-prevention data. Dihexa and P21 have been tested only in animals. BPC-157's human literature consists of three small non-brain studies totaling 30 people. None of these substances is FDA-approved for any cognitive use, and the July 2026 advisory-committee votes on compounding were non-binding.

Animals, Products, and Unknowns

The next refusal concerns translation from experimental systems to people. Dihexa and P21 appear in discussions because preclinical ideas about neural growth and repair are compelling. In the evidence assembled here, neither has a documented human cognitive-outcome trial. Their grade is D: preclinical only for the claim at issue. “D” is not a judgment that an animal result was meaningless. It says the result has not crossed the boundary into a demonstrated human cognitive benefit.

The distinction matters most when a mechanism seems unusually close to the disease. Memory depends on functioning neural circuits; Alzheimer’s disease damages them. It is easy to reason that a substance affecting neural connections in an experimental model must help preserve memory in a person. But the model may not reproduce the human disease, and a short-term biological change may fail to yield a durable benefit. A mechanism can justify asking a research question without supplying its answer.

A February 2026 forum exchange made the uncertainty visible without resolving it. Steve_Combi wrote of Dihexa, "Because of the lack of safety studies on DIHEXA and that there may never be any related to the cancer risk it may present".[9] That was a member's concern, not a demonstrated clinical risk estimate. The responsible reading is neither reassurance nor a declaration that the feared outcome has been proved. Human safety and cognitive outcomes for Dihexa have not been adequately established.

This is an uncomfortable form of uncertainty. An unknown risk cannot be entered into a tidy calculation as zero, yet it cannot honestly be assigned a numerical probability without evidence. Readers may mistake the lack of reported human harms for a reassuring safety record. When human studies are missing, however, the absence of a measured harm may chiefly reflect the absence of measurement. The same limit applies to hoped-for benefit.

BPC-157 presents a different category error: treating small human reports outside the brain as though they validate a central-nervous-system claim. An October 2026 systematic review identified three human studies totaling 30 participants: 16 in a knee-pain report, 12 in an interstitial-cystitis report, and two in a safety pilot. The authors rated the evidence very low certainty; the studies addressed noncognitive indications or safety, not prevention of cognitive decline.[10] Small reports without treatment-related adverse events cannot establish safety for a broad population or for long-term brain-focused claims.[10]

Thirty people across three different studies are not thirty observations of the same cognitive outcome.[10] Pooling their head count in casual conversation can make the evidence sound more unified than it is. The two-person safety pilot is particularly ill suited to settling uncommon harms: even a study conducted carefully cannot reveal an event that does not happen to appear in so small a group. The review's authors advised against clinical use outside regulated, high-quality trials.[10]

FDA staff reached a similarly restrained position when evaluating BPC-157-related substances for the 503A Bulks List. In a May 2026 briefing, staff weighed against listing the substances, citing incomplete physicochemical characterization, missing safety and immunogenicity information, and inadequate effectiveness evidence for the use under review, ulcerative colitis. The human literature they identified did not concern cognition.[11] An assessment of ulcerative colitis cannot settle Alzheimer's prevention either way, but the missing safety and characterization information cannot simply be set aside.

For BPC-157 CNS claims, the grade is D/E: preclinical material and hypothesis or anecdote, not a demonstrated human brain outcome. The slash matters. It does not average animal work and enthusiasm into a higher grade. It records two weak lanes that should not be mistaken for a clinical trial. The small human studies belong in a separate, non-brain lane and do not upgrade the CNS claim.[10,11]

There is also a product question, separate from whether a molecule could work under ideal conditions. A non-peer-reviewed April 2026 preprint analyzed a publicly available dataset of 6,441 samples across 14 products marketed as research-grade peptides. Under the authors' specified benchmarks, 41.6 percent to 71.1 percent of samples failed combined purity-and-measured-abundance criteria. Those are study-defined benchmarks applied to a mixed dataset, not regulatory findings on every product and not a BPC-157-specific failure rate.[12]

The range is striking, but its meaning depends on the benchmark and the sampled products. It would be wrong to say that the preprint found 71.1 percent of all peptides unsafe, or that it measured the chance that any one person would be harmed.[12] Failure to meet a purity-and-abundance criterion is a product-quality finding, not a clinical outcome. It raises a separate obstacle to interpreting reports of benefit or harm: uncertainty about what material a report concerns.

The same preprint reported measurable endotoxin in 15 percent of samples for which endotoxin data were available. Fewer than 4 percent of all samples had those data, so the percentage cannot be generalized to the whole dataset or presented as a BPC-157-specific contamination rate.[12] The paper's preprint status and the dataset's limits warrant caution about its estimates. Its underlying concern is still relevant: the name attached to a product does not, by itself, establish its identity, abundance, purity, or suitability for human use.

Quality uncertainty complicates even a seemingly sincere self-experiment. If a person reports benefit, the report cannot reliably separate the proposed molecule's effect from expectation, concurrent changes, natural fluctuation, or uncertainty about the product. If the person reports harm, the same product uncertainty can make it hard to identify the cause. Better record-keeping by an individual does not turn an uncharacterized material into a standardized intervention.

The supply issue should not be romanticized as a problem that clever consumers can solve alone. Reliable identity and consistency require

systems of manufacture, testing, oversight, and accountability; attractive technical language is not a substitute for those systems. The regulatory and evidence questions also remain distinct. A highly consistent product could still be ineffective for cognition. A biologically active compound with a compelling animal result could still have an unacceptable human risk profile. Neither proposition can be settled by availability.

For the gray-market supply chain, see *The Metabolic Frontier*, Chapter 18.

The Compounding Boundary

The legal story in 2026 created an unusually strong temptation to read movement as endorsement. A committee meeting, an FDA briefing, and a change in an administrative category each sound consequential. They are consequential, but only for the question each addresses. None is a randomized dementia-prevention trial. None makes an unapproved peptide an FDA-approved drug.

Apr 15, 2026: FDA announced removal of 12 peptides from 503A Category 2 ("significant safety risks") after nominations were withdrawn (effective about Apr 22). Removal is not listing; there is no lawful 503A basis until FDA lists a substance or grants enforcement discretion.[13,14] The distinction is easy to miss. Category 2 removal changed an adverse administrative designation; it did not supply the affirmative legal basis needed for 503A compounding. Reading it as a clearance reverses the meaning of the missing step.

PCAC July 23–24, 2026: the advisory committee voted (non-binding) to recommend 503A bulks inclusion of BPC-157 (8–6–1), KPV (8–6–1), TB-500 (8–6–1), MOTS-c (7–5–2), Semax (8–5), Epitalon (7–5–1); it rejected emideltide/DSIP (6–7–1). FDA staff had recommended against all seven. As of late September 2026 FDA had not issued a proposed rule, interim Category 1 placement, or enforcement-discretion policy. None is FDA approved. (As of October 10, 2026 FDA had posted no minutes.)[11,13,14,15]

Those votes were recommendations, not final agency action. The favorable BPC-157 and Semax votes were narrow enough to show disagreement on the committee, and FDA staff's assessments remained part of the public record.[11,14,15] A narrow vote need not mean that committee members disagreed about every underlying fact; they may have weighed uncertainty differently. It cannot be translated into a percentage chance that a peptide

works. The committee was asked about placing particular bulk substances on a compounding list, not whether the peptides prevent dementia. For Semax, the uses FDA evaluated were cerebral ischemia, migraine, and trigeminal neuralgia; dementia prevention and cognitive enhancement were not under review.[16]

The staff review of Semax helps explain why a favorable advisory vote should not be mistaken for a resolved efficacy question. FDA staff proposed against adding Semax free base or acetate to the 503A Bulks List. For the evaluated uses, staff found insufficient effectiveness evidence; they also noted gaps relevant to product standards and immunogenicity.[15] A committee can weigh competing considerations differently from staff. Its vote does not retroactively create the missing studies, and it does not answer an unexamined Alzheimer's question.

Nor is permission to compound, if ultimately granted for a substance, the same as FDA approval of a finished drug. These processes ask different legal and scientific questions. Drug approval evaluates a product for specified uses under an approval framework; a bulks-list decision concerns whether a substance may meet a condition for certain pharmacy compounding. The distinction persists even when the same chemical name appears in both discussions. The absence of a final listing decision in the status record leaves this chapter no basis to describe the July recommendations as authorization.[13,14]

For why compounding is not generic manufacturing, see *The Metabolic Frontier*, Chapter 16.

As of October 2026, the FDA meeting page listed documents and presentations but no posted minutes or final agency action.[13] A later rule or policy would have to be read on its own terms. It would not, by itself, alter the results of CARS, establish human safety or cognitive benefits for Dihexa, or convert BPC-157's non-brain reports into cognitive outcomes.[6,10]

There is a second trap in the language of access. A rule addressing whether a substance may be used in a particular compounding framework would not answer whether an individual finished product has demonstrated clinical benefit for dementia prevention. Nor would a favorable legal change settle the product-quality concerns raised by a mixed-peptide preprint.[12] These questions touch one another, but they require different evidence. Treating any one answer as a substitute for the others gives a regulatory event more scientific weight than it can bear.

The forum's long thread began with descriptions of self-experiments, a familiar form of conversation among people trying to understand an uncertain field.[1] Research asks for a harder comparison, while law asks a different question again. Keeping the three records separate is the discipline this gray zone requires. For Semax and Selank, and for Cerebrolysin, dementia prevention remains Insufficient. Dihexa and P21 remain D for preclinical evidence; BPC-157's CNS claims remain D/E. A post-stroke score, an animal result, a small non-brain human report, a product label, and a non-binding vote cannot be added together as though they were successive measurements of the same outcome.[4,6,7,10,13,14]

The people in the discussion were looking for something medicine cannot yet promise: a dependable way to keep the brain working as the years pass. Taking that wish seriously does not require treating every available compound as a plausible answer. It requires leaving each finding where it belongs, including findings that disappoint, and recognizing when the most accurate result is still an unanswered question.

Chapter 14: The Physician's Protocol



On January 24, 2025, DrFraser opened a public forum thread with a document he wanted other people to challenge. “Here is my protocol right now for Dementia risk reduction, particularly on those with ApoE4’s,” he wrote. “I want community input on this on items I’ve missed or have wrong.” His stated hope was that the discussion would improve what he offered his patients.[1]

What followed was dense enough to read like working notes for a physician: lifestyle considerations, measurements, drugs, and supplements, gathered under the name of dementia risk reduction.[1] The striking feature was not any single entry. It was the invitation to strangers to edit the whole undertaking in public. A reader could see both the appeal and the hazard immediately. An open document can catch errors. It can also grow every time someone brings a plausible new mechanism to the table.

DrFraser had a personal reason to care about APOE ε4. In the thread, he said that both his parents carried a copy, his sister and nephew each had two, and he had one. He also described plans to make public material about the subject.[2] Those are his accounts, not an independently verified family history or an interview conducted for this book. They help explain the urgency of the post without establishing that its contents work. A physician facing risk in his own family can be both unusually attentive and unusually susceptible to the thought that one more intervention might matter.

The thread developed an argument that reaches beyond DrFraser’s document. When does a set of responses to measurable risks become a

protocol, and when is it simply a pile? The question becomes sharper when the promised outcome is protection against Alzheimer's disease. A favorable change in blood pressure, sleep, or a laboratory value is not the same event as preventing dementia; improvement in someone already impaired is a different claim again. This chapter follows the public protocol as a case study, then reads the best controlled claim for a much more widely promoted precision-medicine program against what its comparison actually found.

The Public Protocol

The January post asked for criticism, and criticism arrived quickly. One member proposed a supplement on the basis of what the member called "(weak) evidence"; another wanted greater attention to blood pressure.[3,4] DrFraser did not treat every suggestion as a missing piece. Replying to one proposed addition, he wrote, "I don't think it is disease modifying," then acknowledged, "this is low evidence zone." He said he was holding back a planned video while the community weighed what belonged in or out.[5] The exchange shows a useful feature of an open protocol: a reader can watch its author distinguish a conceivable benefit from evidence for changing the course of disease.

It also shows how hard that distinction is to maintain at scale. Each contributor may be making a modest claim. One asks whether a nutrient belongs on the list; another raises a biomarker; another offers a mechanism connecting two bodily systems. Together, modest proposals create a large implied claim: that attending to enough pathways will reduce dementia risk. The inference is not established merely because no single proposal sounds extravagant. A protocol needs a reason to prefer one response over another, an account of competing harms, and a way to find out whether the added complexity helped.

DrFraser sometimes pushed back on precisely this point. Asked about choline, he said he was struggling over whether to include it and doubted that it affected the "likelihood of disease, which is what I'm aiming for."[2] That last clause identifies an endpoint more demanding than general brain health. It is relatively easy to find reasons that a substance matters to normal physiology. Showing that an intervention changes a person's likelihood of developing Alzheimer's is another matter. A deficiency, a risk marker, and a treatment target are not interchangeable categories.

Another member looked at the length of the document and called it “a gigantic list,” while observing that different causes of cognitive impairment may overlap.[6] That observation cuts both ways. It makes a single-mechanism answer look inadequate, but it does not mean a larger list has been validated. Vascular injury and neurodegenerative disease can coexist. So can an intervention’s intended effect and an unwanted effect. The broader the plan, the harder it becomes to tell which change produced a later result, or whether a problem arose from an item that seemed harmless on its own.

The personal context matters here. DrFraser’s account of his relatives did not make him a representative patient, and his professional title did not turn his post into a guideline.[2] Yet neither point makes the thread frivolous. Its participants were trying to reason under uncertainty while time felt consequential. A forum lets someone expose an unfinished judgment to readers who might catch an omission or challenge an attractive but weak paper. It offers no assurance that the objections will be proportionate, that quiet readers will be represented, or that the final document will have undergone the processes behind a clinical guideline.

Book One, *The Longevity Operating System*, Chapter 13, examines supplement accumulation and the forum effect in greater depth. The distinction matters in this thread because revision can mean removal as well as addition. DrFraser’s willingness to ask whether something was disease-modifying is more informative than the sheer breadth of his opening document.[5] Even so, an openly revised list remains one person’s judgment. Its public history makes the reasoning inspectable; it does not establish that the protocol changes outcomes.

This is where a different physician’s program enters the story. Dale Bredesen’s MEND approach, later associated with ReCODE, likewise treats cognitive decline as a problem that may require attention to many contributors rather than one drug target.[7,8] The resemblance is conceptual, not an assertion that DrFraser’s forum document and the branded program are identical. Both invite a tempting argument: if several components make sense separately, perhaps their combination can do something no component has demonstrated alone. That argument can motivate a study. It cannot replace one.

Cases, Criticism, and Costs

Bredesen's 2014 paper gave the combination approach its most arresting early result. It described ten people with Alzheimer's disease, amnestic mild cognitive impairment, or subjective cognitive impairment who underwent a complex program. The author reported subjective or objective improvement in nine; the person reported not to improve had very late-stage Alzheimer's. Reported changes began within three to six months, and the longest follow-up in that initial paper was two and a half years. The authors themselves called for a larger trial.[7]

Those details explain why the paper traveled. Nine apparent improvements among ten people with feared cognitive problems make a memorable story. They do not make the study controlled. There was no randomized comparison able to show what would have happened to similar people over the same period without the program.[7] The group also combined distinct starting conditions. Subjective cognitive impairment, mild cognitive impairment, and diagnosed Alzheimer's disease are not interchangeable outcomes or necessarily points on one predictable path. If participants improve on a test or report doing better, the observation deserves attention. It does not, by itself, identify the program as the cause or prove reversal of Alzheimer pathology.

Multicomponent interventions present an additional problem even when change is genuine. If sleep, physical activity, diet, medical care, and other elements shift together, which part mattered? Perhaps several did; perhaps participation brought closer clinical attention or more practice with cognitive testing. Without a comparison group, the paper cannot resolve those possibilities. Nor can an impressive response in selected cases establish how often an eligible patient would improve. This is the evidentiary cost of a design that lets the clinician adapt many things at once: the intervention may feel more responsive to an individual, while the resulting report becomes harder to interpret.

A 2024 paper offered seven selected patient histories with reported sustained improvement during a personalized precision-medicine protocol. In some cases, follow-up extended beyond a decade. Its authors explicitly said the case series had no denominator: it could not establish what proportion of all treated patients improved or maintained improvement. They called for long-term cohort work to answer that question.[9] Long follow-up can make a case compelling, especially when a family has lived through years of uncertainty. It does not turn selected cases into a

randomized replication. The report remains in the same broad evidentiary lane as the earlier series: human observations capable of generating questions, not a controlled estimate of benefit.

The Alzheimer Society of Canada has been direct about the stakes of confusing those lanes. In 2023 it said the claim that the Bredesen Protocol reverses Alzheimer's disease had not been proven and that anecdotes were not enough to establish efficacy. It also allowed that some lifestyle changes included in the program might support quality of life. Its objection was to carrying that reasonable possibility across the much larger gap to a claim of reversal or cure.[10] That is a fair distinction, not a dismissal of ordinary health measures or of families who saw meaningful changes.

Money makes the distinction less academic. The Society warned that testing, supplements, special diets, and related services could cost thousands of dollars or more and might not be covered by health plans.[10] A 2025 *New York Times* report described clinicians' concerns about limited evidence for reversal claims, along with the financial and practical burden on a family trying the program; Bredesen acknowledged that total costs could be high. The article is reported journalism, not a trial or a systematic review, and its families cannot establish an average outcome. It does show what the burden can look like outside a study report.[11]

"False hope" can sound like a judgment on the people who buy such services. It is better understood here as a concern about the strength of the promise made to them. A family confronting cognitive decline may reasonably value attention, structure, and the feeling that someone has examined possible contributors. Some participants may also experience benefits worth describing. The ethical problem arises when those experiences are presented as proof that a costly package reverses Alzheimer's. Expense and effort can intensify the pressure to interpret a good month as confirmation; they can make it harder to stop when the hoped-for change does not arrive.

Cost is more than a bill. A complex program consumes time, administrative attention, and the cooperation of relatives who may already be managing care. The fact that several components are familiar does not make the combined burden ordinary. Testing may create findings that require interpretation; supplements add uncertainty about benefit and adverse effects; special diets can be difficult to sustain.[10,11] Book One, *The Longevity Operating System*, Chapter 17, addresses safety, consent, and stopping

rules for such decisions. In the present case, those concerns deserve a place beside efficacy, not a footnote after it.

For a time, critics and supporters could point at the same hole in the evidence. Supporters could say that cases were promising and that a complex intervention deserved a proper comparison. Critics could say the cases had not supplied one. The April 2026 preprint changes the discussion because it reports a randomized comparison. It does not settle every question, but it makes it possible to ask a more exact one: what improved relative to standard care, on which measures, and with what degree of certainty?[8]

The Preprint's Actual Comparison

As of October 2026, version 3 of “Precision Medicine Treatment of Alzheimer’s Disease: Successful Randomized Controlled Trial,” posted April 20, 2026, remained a preprint labeled as not peer-reviewed. Its title states the authors’ interpretation; publication stage matters because its methods, analyses, and claims had not yet passed journal peer review.[8] “Randomized” is still an important advance over selected cases. “Successful,” however, has to be unpacked endpoint by endpoint.

The authors reported 73 participants, ages 45 to 76, with mild cognitive impairment or early dementia at six sites. Over nine months, 50 were assigned to precision medicine and 23 to standard care; seven assigned to precision medicine dropped out.[8] These are people who already had cognitive symptoms, not adults without impairment being followed to see whether dementia could be prevented. A result in this population cannot establish that the full program prevents Alzheimer’s disease in a person who currently has no symptoms.

The preprint reported advantages for the precision-medicine group on several computerized cognitive measures, including memory, executive function, and processing speed. It also reported that the between-group difference on the Montreal Cognitive Assessment, or MoCA, was not statistically significant. Mean MRI volume changes did not differ significantly between groups either. The authors called for a larger randomized, double-blind, placebo-controlled trial.[8] An accurate account has to hold the favorable computerized results and the null comparisons in view at the same time.

The MoCA finding is particularly useful as a check on a sweeping headline. It does not prove that nobody benefited, or that every computerized measure was noise. Nor does a nonsignificant result prove that the true difference is exactly zero. It says that this comparison did not demonstrate a statistically significant between-group advantage on that endpoint over the trial's nine months. The MRI result similarly offers no statistically significant between-group difference in mean volume change, rather than imaging confirmation of reversal.[8] Selective quotation of only the favorable measures would make the result sound cleaner than the reported comparison permits.

There are several reasons a trial can yield mixed measures without anyone behaving improperly. Tests capture somewhat different abilities, vary in sensitivity, and contain measurement noise. A nine-month study may be too short for some changes to emerge clearly. An unequal allocation and dropouts make the precise handling of missing data worth examining. Equally, testing several outcomes creates more opportunities for an apparently favorable finding. None of those general cautions is a verdict on this preprint. They explain why its complete analysis, peer review, and independent repetition matter more than the word *successful* in its title.[8]

The design also leaves a practical question about attribution. A randomized comparison can test whether assignment to the package produced different measured outcomes from assignment to standard care. It cannot, without further design work, identify a single ingredient responsible for a difference. That limitation is not unique to ReCODE; it is inherent in a package assembled from multiple changes. If the package is the product being defended, evidence about that package is exactly what matters. But a positive result on one test would not validate each supplement or measurement within it, just as a null result on another test would not show that physical activity or attentive routine medical care lack value.

The grade here must attach to a stated claim. For Bredesen/ReCODE as a way to reverse Alzheimer's disease or prevent dementia, the evidence is C at best: C means observational or uncontrolled human data, and the case reports occupy that lane. The preprint supplies a B-null MoCA comparison: B-null means controlled evidence of no effect demonstrated on the endpoint tested, within the limits of that comparison. Its selected favorable computerized outcomes remain reported controlled signals awaiting peer review and replication; they do not erase the null MoCA result or establish the larger prevention claim.[7,8,9] A grade is not a vote on whether the people

reporting improvement were sincere. It states what kind of claim the available design can bear.

This distinction also protects against an unfair reading in the opposite direction. A null MoCA comparison in a small study of symptomatic participants is not proof that a healthier diet, better blood-pressure care, or more activity is pointless. The National Institute on Aging said in July 2026 that nothing had yet been proven to prevent Alzheimer's disease, while describing management of blood pressure, physical activity, and other general health measures as reasonable.[12] Ordinary components can have reasons to exist independent of a branded program. That is not evidence that assembling them under one name reverses established disease.

Protocol Versus Pile

Return to DrFraser's January thread. Its best feature was not the quantity of material he put before the forum, but his invitation to remove what was wrong and his occasional refusal to promote a plausible addition into a disease-modifying one.[1,5] A protocol, in the stronger sense, makes its priorities and uncertainty visible. A pile can contain many sensible items and still lack an answer to the question that matters: what extra benefit does the whole arrangement produce, compared with competent care that does not include the arrangement?

The forum could interrogate one claim at a time. A member could question a supplement, argue for attention to a familiar risk factor, or ask whether an addition addressed disease likelihood at all.[2,3,4] What it could not do by discussion alone was supply the missing counterfactual. If a participant later felt sharper, the thread would not show what that person's cognition would have been without the changes. If several measures improved, it would not establish which changes mattered. If nothing improved, the sheer number of moving parts would invite one more proposed correction.

Bredesen's papers illustrate successive attempts to get closer to that counterfactual. The 2014 ten-person report made an observation worth investigating but had no control group. The 2024 seven-person report offered unusually extended accounts but no denominator for estimating how often they occurred. The 2026 preprint introduced random assignment and reported favorable selected computerized measures alongside a nonsignificant MoCA comparison and no significant difference in mean MRI volume change.[7,8,9] Each design answers a narrower question than the public phrase "reversing Alzheimer's" suggests.

The disagreement is therefore not between people who care about prevention and people who do not. It is about what counts as evidence when the hoped-for outcome is so consequential. A family can value a clinician's attention without purchasing certainty. A forum can improve the questions asked of a public document without validating the document as clinical practice. And a controlled signal on selected tests can warrant further study without proving that a branded combination prevents dementia or reverses Alzheimer's disease.[8,10,12]

DrFraser's post remains a dated record of a physician asking others to inspect his thinking, not a validated outcome for his patients.[1] Read that way, it earns respect without being mistaken for proof. The most productive question it poses is not what else can be added. It is whether the next addition has earned its place, and whether the claim attached to the entire package is one that anyone has actually tested.

Chapter 15: Rapamycin's Fast Lane



The disagreement was not about whether rapamycin had an interesting biological story. It did. The disagreement was about how far that story could run ahead of the brain trials. A small imaging study in cognitively normal people with an Alzheimer's risk gene appeared to point one way; short studies in people who already had symptoms raised different, and sometimes troubling, questions. The forum's proposed explanation was that *stage* mattered: perhaps an intervention could help before symptoms while offering no benefit, or even causing harm, afterward. That was an explanation worth testing, not a result.

There was a second uncertainty underneath it. If rapamycin changed a brain scan, had the drug acted inside the brain? Had it changed blood vessels or immune activity elsewhere, with an indirect effect on the scan? Or had a small, uncontrolled study simply captured variation that would not survive comparison with a placebo group? The blood-brain barrier made these more than academic questions. The forum argued about whether rapamycin crossed it in meaningful amounts and whether a barrier altered by age, genotype, or disease might change the answer. None of those arguments established who, if anyone, stood to benefit.

This is an abbreviated account of a long discussion: one stage hypothesis, two limited human signals, and an awaited controlled test. The pace matters. A biological proposal can be assembled from animal work, a few scans, and a lively thread much faster than investigators can measure whether people retain memory and function.

Stage Is a Hypothesis

Rapamycin, also called sirolimus, entered medicine for purposes other than protecting memory. As of October 2026, its approved uses do not include aging or dementia prevention; using it for those aims is off-label, a question for a clinician rather than a regimen established by this book's evidence. For the fuller account of mTOR biology, see *mTOR, Metabolism, and Muscle*, Chapter 1. For rapamycin's approved uses and labeling, see *mTOR, Metabolism, and Muscle*, Chapter 4.

The attraction of the stage hypothesis is easy to understand. Alzheimer's-related changes can develop before a person notices trouble with memory, while a person with mild cognitive impairment or dementia may have several forms of injury already underway. An intervention that alters one early process need not reverse later losses. The converse is also possible: an early intervention might change a marker without improving anyone's future, while a treatment in symptomatic disease could still help on a different endpoint. Stage is a proposed modifier of effect, not a synonym for "earlier is always better."

The forum's comparison began with reports from cognitively normal APOE ε4 carriers and reports involving people with mild cognitive impairment or Alzheimer's disease. In a January 2026 discussion, CronosTempi set out one possible reason for an APOE-related difference: "it can have effects outside the brain that nonetheless affects the brain even if rapamycin itself doesn't cross the BBB." The post also proposed that differences in barrier integrity could matter. It was a hypothesis about where a signal might come from, not evidence that an indirect effect had protected cognition.[1]

A barrier account faces an awkward alternative. If the drug's effect depends on entering a brain whose barrier is already more permeable, an observed difference between groups might reflect exposure rather than a beneficial correction of APOE4 biology. If it acts through the circulation instead, finding little drug in spinal fluid would not, by itself, rule out a brain effect. Neither possibility licenses an inference from a scan to a useful clinical outcome. It also makes simple comparisons between studies hazardous: the groups may differ in genotype, symptoms, underlying pathology, vascular health, and the measurements investigators chose.

A sharp moment in the discussion came when adssx compared the asymptomatic imaging report with an earlier study in people with symptoms that had raised concern about cognitive scores. "These are two different studies so we cannot conclude at this stage," adssx wrote. Only

then came the suggestion that rapamycin might behave differently before and after symptoms. That first sentence is the restraint the later hypothesis requires.

The statistical distinction is plain even if the biology is not. A favorable change in one small group and an unfavorable change in another do not prove that disease stage caused the difference. To test that claim, researchers would need comparable definitions of stage, a treatment comparison within each group, sufficiently large groups, and an explicit test of whether the treatment effects differ. Two studies conducted separately can suggest the question. They cannot answer it merely by pointing in opposite directions.

"Symptomatic" is not a single biological state, either. Mild cognitive impairment is a clinical description with more than one possible cause. Cognitively normal people carrying APOE4 are not interchangeable with one another: some may already have measurable Alzheimer's pathology and others may not. Even among carriers, having one copy of the allele is not the same as having two. A 2024 pathology and clinical analysis drew on 3,297 brains and 10,039 people and found an unusually consistent Alzheimer's-biology pattern in APOE4 homozygotes; by age 65, nearly all had abnormal spinal-fluid amyloid, and 75 percent had positive amyloid scans. That finding describes a particular genetic group. It does not establish that a drug affecting a scan in a few carriers will prevent dementia in that group, much less in every adult worried about dementia.[2]

The forum had found a disciplined question inside a tempting narrative. Did treatment response differ by stage, genotype, or some feature that traveled with them? The answer would require people, outcomes, and controls rather than a more elaborate account of the blood-brain barrier. For how a separate trial, PEARL, tested rapamycin against broader healthspan measures rather than dementia prevention, see *mTOR, Metabolism, and Muscle*, Chapter 5.[3]

An APOE4 Imaging Signal

The Missouri research program gave the stage argument a tangible, if preliminary, signal. Early reports described changes in brain volume or blood flow among a very small number of cognitively normal APOE ε4 carriers, without a comparable pattern among a few non-carriers. A larger open-label pilot later described 23 adults, nine carriers and 14 non-carriers, and reported carrier-related changes in cerebral blood flow over a short follow-up. Part I findings appeared in a peer-reviewed report in September 2026, but the study registry posted no results as of October 2026. A separate randomized study in asymptomatic APOE ε4 carriers was recruiting; it had not established whether the imaging changes translate into cognitive benefit.[45]

What can be said about the reported signal is narrower than "rapamycin helped APOE4 carriers." Imaging estimates blood flow or the boundaries of a structure. Those measurements can help researchers see where to look next, but they are not direct observations of preserved memories. In a small open-label study, a change from before to after exposure also lacks the most useful counterfactual: what would have happened to similar participants who had not received the drug? Scan acquisition, analysis choices, ordinary biological variation, and chance can matter greatly when a subgroup contains only a handful of people.

The genetic focus adds another limit, not a special exemption from the need for controls. The Missouri comparison concerned people selected in part by APOE status, with especially small numbers in each group. A signal in carriers cannot simply be carried over to non-carriers, to older adults with different vascular burdens, or to everyone with a family history of dementia. Nor would it necessarily apply equally to people with one and two APOE4 copies. The large 2024 analysis of APOE4 homozygotes helps show why genotype can matter for Alzheimer's biology, but it did not test rapamycin.[2]

There is a useful contemporary contrast. A 2026 meta-analysis harmonized three randomized *lifestyle* trials involving adults aged 60–85 and found that APOE4 status modified the intervention's effect on global cognitive scores at 12 months; the reported difference appeared more closely tied to executive function than to memory or processing speed. At 24 months the interaction was borderline, and the trials did not establish an effect on dementia incidence. This is evidence that genotype can sometimes modify a

measured response. It is not corroboration of the Missouri rapamycin finding: the interventions, populations, and endpoints differ.[6]

The danger is an upgrade by association. A gene is linked to risk; an imaging measure changes in carriers; a separate body of work finds a genotype interaction for lifestyle; therefore the drug must be protecting a genetically vulnerable brain. Each step adds a claim the preceding study did not test. If the Missouri signal replicates under randomization, investigators will still have to determine whether the imaging change is reliable, what produced it, and whether it predicts something people can feel or do years later.

That distinction also cuts against dismissing imaging altogether. A carefully measured scan can reveal an unexpected effect and help a research team decide what to examine in a larger trial. A null scan can challenge a proposed pathway. Its proper role here is to sharpen the next experiment, not to stand in for the experiment's eventual clinical answer. The Missouri account merits attention precisely because a genotype-linked imaging finding is testable. It does not deserve a prevention claim in advance of that test.

ERAP's Mixed Picture

ERAP offered a different human signal, this time in people with early symptomatic Alzheimer's disease. The small, single-arm, open-label study enrolled 14 people, 13 of whom completed follow-up. Without a concurrent control group, changes over time cannot be assigned confidently to rapamycin. The reported prespecified regional FDG-PET measures did not improve, while exploratory imaging findings pointed in more favorable directions. Several spinal-fluid biomarkers associated with neuronal or other brain injury also increased. Summary results were posted in the EU clinical-trials register in October 2025 and the main report appeared as a preprint in December 2025; as of October 2026, no peer-reviewed primary-results paper had been published and ClinicalTrials.gov showed no results.[7]

The forum did not treat the mixed picture as a clean success. On March 5, 2026, RobTuck called the pilot "a credible first step" toward a controlled design, then added: "the CSF biomarker pattern is definitely not the minor interpretive footnote it is assigned in this preprint." That judgment did not turn a biomarker rise into proof of harm. It refused to hide an uncomfortable result behind an interesting scan.[8]

There are competing readings of those fluid markers. A rise might reflect injury, altered release from cells, altered clearance, or a process the available measurements cannot distinguish. Some forum discussion favored a "cleansing" interpretation: perhaps material appeared in spinal fluid because the intervention was moving it out of tissue. That account is a conjecture, not a demonstrated benefit. Equally, calling every rise drug-caused damage would go beyond what an uncontrolled pilot can establish. The unresolved point is not whether an imaginative explanation exists. It is whether a controlled study can connect a reproducible marker pattern to better or worse cognition and function.

ERAP's design makes the distinction between *primary* and *exploratory* findings especially consequential. A prespecified outcome states in advance what result the study is chiefly positioned to assess. Exploratory comparisons can locate patterns worth pursuing, but the more regions and markers examined, the easier it becomes to find an apparently favorable movement by chance. A pre-to-post increase in a selected region does not cancel a null prespecified result. Nor can stability on a metabolic scan be called disease stabilization without knowing how a comparable untreated group changed over the same period.

The symptomatic population matters as well. ERAP cannot directly settle a claim about prevention in cognitively normal carriers. But neither can the Missouri account make ERAP's biomarker pattern disappear. If the stage hypothesis is right, investigators must demonstrate the difference rather than assigning every favorable observation to "early" and every unfavorable one to "late." That is a theory protected from failure, not a theory subjected to a trial.

One forum post captured the tension without pretending to settle it. On March 4, 2026, CronosTempi wrote, "Preprint, but super exciting!" and then, "Early days, but I hope more to come." Warmth toward that hope need not soften the evidentiary line. People confronting Alzheimer's disease have good reason to notice even a small human study. They also bear the costs when a preliminary result is made to sound more conclusive than it is.[9]

Rapamycin/sirolimus therefore carries a C/D headline for the claim that matters here, preventing dementia or slowing cognitive decline in at-risk adults without dementia, and its prevention outcome remains unresolved. On this series' scale, C means observational or uncontrolled human data, while D means preclinical evidence only. Neither grade means that a

favorable brain scan or a biological rationale has demonstrated clinical prevention. ERAP belongs in the limited, uncontrolled-human lane; the broader prevention story cannot be promoted by borrowing confidence from animal work or from a different population.

What REACH Must Settle

REACH is the awaited controlled test in this chapter's short sequence. Registered in people with amnestic mild cognitive impairment or early Alzheimer's disease, it includes a placebo comparison and cognitive, functional, imaging, and safety measures. Those features address weaknesses that no amount of reanalysis can remove from a single-arm pilot. As of October 2026, the registry listed REACH as active but not recruiting, with 40 participants enrolled and no results posted. Its primary completion date had passed, but that is not a finding.[10]

Randomization would make a specific kind of answer possible. If an imaging measure changes more in the rapamycin group than in the placebo group, researchers can be more confident that the assigned intervention produced the difference. They would still need to ask whether that difference accompanies a meaningful change in cognition or daily function, and whether adverse effects alter the balance. If clinical measures do not improve, a scan may remain a biological observation rather than a reason to use the drug for Alzheimer's disease. If clinical measures worsen, an attractive mechanism cannot overrule them.

The standard for an eventual upgrade is illustrated, with strict limits, by trials of established *symptomatic* Alzheimer's treatments. CLARITY AD enrolled 1,795 people with amyloid-confirmed mild cognitive impairment or mild dementia due to Alzheimer's disease; over 18 months, decline on the Clinical Dementia Rating–Sum of Boxes was 1.21 points with lecanemab and 1.66 with placebo. The trial also found amyloid-related imaging abnormalities with edema in 12.6 percent of lecanemab recipients versus 1.7 percent of placebo recipients. Those are measured clinical and safety outcomes in a defined symptomatic population, not evidence that lecanemab, or rapamycin, prevents dementia in people without symptoms.[11]

TRAILBLAZER-ALZ 2 likewise studied early symptomatic Alzheimer's disease, enrolling 1,736 people with amyloid and tau pathology. In its low- or medium-tau group, worsening on the same clinical scale over 76 weeks was 1.20 points with donanemab and 1.88 with placebo; edema-type

imaging abnormalities occurred in 24.0 percent and 2.1 percent, respectively, and three treatment-related deaths were reported. These trials are outcome comparators, not endorsements of treating asymptomatic adults. Their lesson for this chapter is methodological: an intervention's favorable biology must be weighed alongside a clinical difference and its harms, in the population actually studied.[12]

REACH, even if it produces a clear result in early symptomatic disease, will not by itself prove the Missouri prevention hypothesis. Its participants and endpoints must be read as registered and reported. A result in one disease stage cannot simply be reversed to predict the result in another. A convincing stage claim would ultimately require controlled comparisons that define stages consistently and test whether treatment effects truly differ. Until then, the blood-brain-barrier debate and the genotype-specific imaging account remain reasons to design research, not grounds for a regimen.

The forum's speed had value. Members found small reports, challenged optimistic readings, and kept asking when controlled results would arrive. Its speed also created the temptation at the center of this chapter: to let a plausible explanation finish the work that a clinical trial had only begun. The evidence-grade boundary leaves room for curiosity without mistaking it for an answer.

Status as of October 2026

As of October 2026, the Missouri program had reported Part I imaging findings but posted no results for its larger study; a separate randomized study was recruiting. ERAP had reported mixed findings, with summary results in the EU trial register and the main report still a preprint, while REACH had posted no results. None had shown that rapamycin prevents dementia or slows cognitive decline in at-risk adults without dementia.[3,610745]

Chapter 16: The Memory Drug Nobody Expected



A beautiful mouse result entered a public longevity forum in May 2022. Within days, it had acquired a human promise the experiment had never made. Researchers had found that blocking a receptor could restore one kind of memory performance in middle-aged mice; maraviroc, an approved HIV drug, could do the blocking. The forum posted the story on May 28, three days after the paper appeared in *Nature*.

The leap was understandable. An unfamiliar laboratory compound might have remained an interesting mechanism. A medicine already used in people sounded like a shortcut past years of drug development. Yet “used in people” answered a safety and regulatory question in a particular disease. It did not answer whether the drug preserved memory in adults growing older without HIV, much less whether it prevented Alzheimer’s disease.

Over the following years, members returned to maraviroc from different directions: brain repair, physical stamina, Long COVID, and cognitive performance. Some reported changes; others reported disappointments or raised placebo as an explanation. Their candor makes the archive worth reading. It cannot turn a mouse experiment, a handful of self-observations, and a study in another human population into a prevention finding.

The Mouse Result's Appeal

The 2022 experiment concerned *memory linking*. When two experiences occur close together, overlapping groups of neurons can help one memory call up the other. In middle-aged mice, increased signaling through the receptor CCR5 was associated with a shorter period in which experiences could be linked. Blocking CCR5 with maraviroc, or reducing receptor expression genetically, improved performance on the laboratory task. These were findings in mice, not evidence that maraviroc improves human memory.[1]

This was a result about a defined task, not an animal diagnosed with Alzheimer's disease. Laboratory memory linking is not interchangeable with delayed verbal recall, managing finances, or remaining free of dementia. CCR5 also participates in immune signaling, so the finding did not establish that less CCR5 activity is uniformly better. The detailed mechanism belongs elsewhere in the series. Here, the question is what happened when a narrow preclinical result began to stand in for a broad human claim.

The forum's first burst of interest did not immediately become a steady stream of accounts. The sampled July archive showed little activity between 2022 and 2025, followed by a cluster of self-experimentation in late 2025 and early 2026. A mainstream feature on related brain-repair work helped revive attention. One member advanced a claim about people with a genetic change resembling CCR5 blockade; in the archive, that was a member's synthesis, not an independently established result for dementia prevention.

The accounts that followed did not even pursue a single endpoint. A member who had come to maraviroc through Long COVID later described slight improvement in some symptoms and no improvement in the fatigue and exercise limitations that mattered greatly to him. Another member, interested in working memory, repeated a cognitive test after trying the drug and recognized that familiarity with the test could explain part of the apparent gain. Others discussed physical stamina. These were distinct observations, under different conditions, made without blinded comparisons. None measured Alzheimer's incidence or sustained cognitive decline.

The working-memory account is especially instructive because the member had attempted a baseline and had thought about practice effects. That is more informative than a bare assertion that memory felt sharper. It still leaves expectation, ordinary variation, measurement error, and repeated

exposure to the test competing with a drug effect. A large change in one person's score can be real as an observation without being attributable to the proposed cause. The forum's willingness to consider placebo improved the honesty of the record, not its evidentiary grade.

For cross-population evidence appraisal, see Book One, *The Longevity Operating System*, Chapter 2, "The Hierarchy of Evidence." The point here is narrower than a general lesson about animal studies: maraviroc already had a controlled human cognitive trial, but that trial enrolled people whose illness and treatment differed sharply from the healthy-aging question.

A Different Human Population

ACTG A5324 enrolled 191 people with HIV-associated neurocognitive impairment whose HIV was suppressed on antiretroviral therapy. Over 96 weeks, participants were assigned to placebo intensification, dolutegravir, or dolutegravir plus maraviroc. Cognitive performance improved across the study, but the groups did not differ in improvement at 48 or 96 weeks. This controlled null result concerns cognition in people with HIV; it does not test dementia prevention in people without symptoms.[2]

A5324 did not randomize cognitively healthy older adults to maraviroc or placebo. It tested adding the drug within antiretroviral treatment for people who already had HIV-associated impairment. The causes of impairment, the accompanying medicines, and the possibility of improvement during follow-up all matter. A result in that setting cannot be stamped onto every population in which CCR5 might have a role. Equally, calling it "the wrong population" and setting it aside would discard the most direct controlled human cognitive evidence in this case.

The across-the-board improvement illustrates what the comparison group contributes. People in all arms can improve while participating in a study: they may become familiar with testing, receive clinical attention, or simply fluctuate from a low starting measurement. Randomization asks whether one assignment produces more improvement than the alternatives. In A5324, adding maraviroc produced no detectable advantage on the cognitive outcomes reported in the July account. That is a narrower, more useful statement than either "maraviroc improves cognition" or "CCR5 has nothing to do with memory."

The distinction also puts the forum observations in proportion. A member's improved retest score and a trial's improvement across every arm are not

contradictory. Both can happen when measured performance changes for reasons other than the intervention of interest. Conversely, A5324 does not prove that every reported individual change was imaginary. It asks a different question: whether assigning this drug, in this studied population, improved cognition beyond the changes seen under the other assignments.

The grade therefore has two lanes. For the headline claim, preventing dementia or slowing cognitive decline in at-risk adults without dementia, maraviroc is D, meaning the directly relevant case here remains preclinical rather than a demonstrated human outcome. For the distinct A5324 population and endpoint, the result is B-null: controlled human evidence of no added effect on the cognition tested. B-null is not a universal verdict on the molecule; D is not permission to promote the mouse result into human prevention evidence.[2]

Maraviroc belongs within its approved antiretroviral context. Its established use does not create an approved cognitive indication, and the case assembled here does not support prescribing it to prevent dementia. Any off-label question belongs with a clinician who can consider the person, the indication, and the drug's risks rather than infer a regimen from mouse work or forum reports. For safety and consent in self-experimentation, see Book One, *The Longevity Operating System*, Chapter 17, "Safety, Consent, and Stopping Rules."

What a Null Can Close

A null result has boundaries, but those boundaries should not make it disposable. If a drug produced a large cognitive enhancement wherever CCR5 was blocked, a 96-week controlled study in people with measured impairment offered an opportunity to observe an added effect. A5324 did not detect one. That constrains the broadest version of the promise, the idea that an approved blocker of a memory-related receptor should generally improve human cognition. It does not close a claim that was never adequately tested, such as an effect confined to a particular recovery window after injury.

That remaining possibility carries a cost in precision. Each proposed exception must specify a population, outcome, and reason the biology might differ. "Perhaps it works in other people" is a possibility, not a result. If it is invoked after every null, without a way to test it, the hypothesis can become impossible to disappoint. A responsible next study would make its distinction clear before the outcome is known.

Intranasal insulin offers a comparison, not an interchangeable mechanism. It had a plausible reason to be studied for cognitive impairment, yet in SNIFF, 289 adults with mild cognitive impairment or mild Alzheimer's dementia were randomized to intranasal insulin or placebo for 12 months. An unreliable first device complicated the study. In the primary, second-device population of 240, change on the ADAS-Cog-12 did not differ between groups; other clinical and cerebrospinal-fluid outcomes did not differ either. The credible central-nervous-system rationale had to meet a controlled clinical endpoint, and the primary comparison was null.[3]

SNIFF cannot predict what a maraviroc trial in healthy aging would find. It shows why a mechanism, even one directed at the brain, remains a proposition until the intended clinical effect is measured. It also shows why the design matters when interpreting disappointment: the device problem limits a simplistic retelling of the whole trial, while the prespecified primary population still supplies a clear null comparison.[3]

A later infectious-disease repurposing study sharpens the point. In VALAD, 120 people who were positive for herpes simplex virus antibodies and had early symptomatic Alzheimer's disease were randomized to valacyclovir or placebo; 93 completed the trial. Over 78 weeks, the primary cognitive outcome worsened more in the valacyclovir group, with a between-group ADAS-Cog11 difference of 3.93 points toward greater impairment. The result did not support valacyclovir as a treatment in that population. It did not, by itself, settle whether herpes simplex virus contributes to the development of Alzheimer's disease.[4]

VALAD's lesson for maraviroc is not that antiviral and antiretroviral drugs share a cognitive fate. It is that a drug's usefulness against an infection, together with a plausible disease hypothesis, does not establish a cognitive benefit. The population, comparator, duration, and measured outcome have to do that work. A harmful result in early symptomatic Alzheimer's also should not be stretched into a finding about prevention in people without symptoms; that would repeat the same cross-population mistake in the opposite direction.[4]

As of October 2026, the National Institute on Aging states that nothing has yet been proven to prevent Alzheimer's disease. That does not mean every candidate is equally unlikely or that research must stop. It does set a high bar for the word *prevention*, particularly when the evidence being offered is a laboratory task, an uncontrolled retest, or a trial conducted for another clinical question.[5]

The Generalization That Remains Untested

The missing test is easy to describe and hard to perform: determine whether CCR5 blockade produces a meaningful, reproducible cognitive benefit in an appropriate population outside the A5324 setting, with outcomes suited to that claim. Prevention would demand more still. A short-term improvement on a memory task would not establish a lower rate of dementia years later, and an effect during recovery from brain injury would not establish protection during otherwise typical aging.

Two registered stroke studies address neighboring questions rather than that prevention claim. MARCH concerns post-stroke cognitive impairment; CAMAROS pairs maraviroc with structured rehabilitation after stroke and focuses primarily on motor recovery, with cognition among its assessments. As of October 2026, both registry statuses are unknown, and neither has posted results. Those records do not establish that either study finished as planned, and their designs should not be treated as completed findings.[67]

Stroke research might be informative because an injury creates a defined period of recovery. It also creates a generalization problem of its own. Repair after a vascular event, performance on a laboratory linking task, HIV-associated impairment, and the slow development of Alzheimer's disease do not share a single clinical endpoint. If a stroke study eventually reports a cognitive benefit, the finding will deserve attention for the people and outcomes it tested. It will not retroactively make the 2022 mice a dementia-prevention trial.

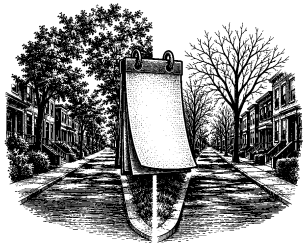
There is a further distinction between the presence of a drug in the body and its effect in the relevant neural circuit. A forum member revisited whether the drug might reach the brain after reporting a cognitive change, an unusually thoughtful effort to examine an alternative weakness in his own story. But a calculation about possible brain exposure cannot establish receptor engagement in the neurons that mattered in the mouse experiment, or prove that an observed retest score arose from that engagement. The July discussion usefully identified a question for researchers; it did not answer it.

The mouse study made maraviroc worth asking about. The forum showed why people found the question compelling and how readily reports gathered around an available drug. A5324 found no added cognitive benefit in a controlled trial involving a different human population, constraining any claim of general cognitive benefit while leaving a more specific

hypothesis open to testing. No one of those observations cancels the others. None establishes dementia prevention.[21]

The members who reported uneven outcomes, considered test familiarity, or named placebo were not failing to understand evidence. They were often describing its limits from inside their own experiments. Their reports preserve what it felt like to encounter an appealing finding before the necessary trials existed. The scientific promise, if there is one, remains a question with a defined burden of proof, not a benefit that the mouse, the forum, or the HIV trial has already delivered.

Chapter 17: Old Drugs and Old Viruses: Lithium, Vaccines, and Antivirals



On August 18, 2025, a forum thread appeared under the title “Alzheimer’s is linked to low brain lithium levels, study shows.” RapAdmin’s reply was brief: “Already discussed a lot.”[1] The news had arrived at a community with a long-running lithium discussion, not a blank slate.[1,2] Researchers had found less lithium in brain tissue from people with mild cognitive impairment or Alzheimer’s disease, and experiments in mice had raised the possibility that restoring it mattered. The treatment findings, however, were in mice, not in people with memory problems.[3]

By September 2026, another thread had a more urgent title: “Should we all be taking low doses of lithium to prevent Alzheimer’s?” Between those two threads, a controlled clinical trial had reported its results. None of its six prespecified main outcomes reached the trial’s significance threshold.[4] The question was no longer whether lithium made an interesting biological story. It was what remained of that story after a human test had failed to confirm a clinical benefit.

Two other ideas followed a related, though not identical, course. A birth-date rule for shingles-vaccine eligibility in Wales offered unusually strong observational evidence linking vaccination with fewer dementia diagnoses.[5] Then a randomized antiviral trial in people already living with early symptomatic Alzheimer’s disease produced not a benefit, but worse cognitive results in the treatment group.[6] Old drugs and old viruses made a persuasive combination: familiar interventions, plausible mechanisms, and

large numbers in the headlines. The three results demanded three different readings.

Lithium's Sudden Appeal

Lithium carries a strange double identity. In clinical medicine it is an established prescription drug, with kidney and thyroid concerns that make casual comparisons to ordinary nutrients misleading.[7] In longevity discussions it can appear as a naturally occurring trace exposure, a possible missing element in the aging brain, or a supplement sold as lithium orotate. These are related ideas, but they are not interchangeable claims. A difference measured in a postmortem brain does not identify the cause of that difference. An association involving drinking water does not show that a supplement prevents dementia. And a salt that sounds chemically different has not thereby demonstrated a different clinical effect.[3,7,8]

The 2025 finding offered the most arresting version of the story. Researchers measured lower lithium in prefrontal-cortex samples from people with mild cognitive impairment and Alzheimer's disease than in comparison samples. They also tested lithium orotate in mice, with findings that drew attention to its possible effects on Alzheimer-related biology. The National Institutes of Health account made the boundary clear: the treatment work was in mice, and research was still needed to establish safety and effectiveness in humans.[3]

The tempting interpretation was *deficiency*. It is a powerful word because it suggests a recognizable remedy: find what is missing and put it back. But lower lithium in tissue collected after cognitive impairment has developed cannot tell us whether low lithium helped cause disease, resulted from disease, or accompanied some other change. Brain tissue may reflect altered handling of metals or differences between the people whose samples were available. Those possibilities do not make the observation uninteresting. They make it a starting point rather than a diagnosis of a missing nutrient.[3]

Mouse experiments sharpened the question while leaving the human answer open. An intervention can alter memory-related measures in a laboratory model without preventing the years-long, mixed-pathology condition that clinicians call dementia. Mice also cannot settle which chemical form would be effective or safe in people. The preclinical result belongs below controlled human evidence, even when its mechanism looks

unusually coherent. On the series scale, animal work is D: useful for forming a hypothesis, not proof of a clinical outcome.[3]

The forum's earlier lithium discussion helps explain why the result traveled quickly. Members had already been examining possible mechanisms and debating what could be inferred from individual experience. In January 2023, John_Hemming wrote, "There does not appear to be much useful data."[9] That sentence has aged better than the certainty sometimes attached to the later headline. Forum testimony can reveal the questions people are trying to answer; it cannot establish whether an intervention changes dementia risk.

Drinking-water studies seem, at first, to offer a way past the mouse problem. They examine people who encountered different background lithium levels without choosing a cognitive supplement. Yet background exposure is difficult to measure precisely, and the places being compared may differ in ways unrelated to lithium. The Scottish cohort illustrates the hazard of treating "water studies" as a single favorable finding. Investigators linked drinking-water measurements from 285 sites to health records for 37,597 older cohort members; 3,605 had developed dementia by June 2012. At the very low lithium levels measured, the study found no association supporting a protective effect. Some results included a trend toward higher risk among women. The authors identified observational design and possible exposure misclassification among the limits.[8]

That null result does not prove lithium has no biological role. Nor should favorable cohorts be discarded because one cohort disagrees. It does mean that "more lithium in water, less dementia" is an unreliable summary of the human evidence. A water-system measurement may be an imperfect stand-in for a person's exposure. Even if an exposure association were consistent, it would not specify a beneficial prescription or establish that lithium orotate has the same effect.[7,8]

As of October 2026, a systematic review had assembled a much larger literature: 23 studies involving more than 1.2 million participants, though only 11 supplied extractable data for its quantitative analyses. Four pooled cohort studies produced a dementia hazard ratio of 0.633, with a 95% confidence interval from 0.517 to 0.775. That is a substantial association, and it deserves to be reported plainly. The review's authors also cautioned that observational evidence cannot establish causality.[10] A hazard ratio describes a comparison between groups, not how many cases a supplement would prevent in a population offered it. Without a suitable baseline risk

and a causal effect, converting that relative association into a promised personal benefit would add an answer the cohorts cannot provide.

The contrast with the Scottish result is not a reason to choose whichever number feels more convincing. It is a reason to ask what the cohorts actually compared, how exposure was assigned, and whether their biases might point in the same direction.[8,10] Pooling studies can make an estimate more precise without curing a shared problem in the studies being pooled. Conversely, disagreement can reveal that the proposed effect depends on exposure range or population. Those explanations need tests; they should not be selected after the fact merely because they preserve a preferred result.

The same review pooled three randomized trials of cognitive outcomes, with 229 participants in total, and reported a modest aggregate signal: a standardized mean difference of −0.410, with a confidence interval barely excluding zero and P=.040. Its literature search stopped at December 2024. Consequently, that randomized synthesis did not include the MCI trial published in March 2026.[4,10] A reader encountering "meta-analysis finds benefit" in September could reasonably assume that the newest, directly relevant trial had been included. It had not. Publication date and search date tell different stories; the latter establishes which evidence an analysis could actually weigh.

Safety makes the distinction consequential. Lithium is not rendered biologically inert by being discussed as a trace element, and recognized concerns include effects on renal and thyroid function. Unsupervised lithium supplementation can pose risks.[7] The precise balance of benefit and harm for dementia prevention has not been established by association studies. Calling a product "natural" does not answer the two questions a prevention claim must face: does it work for the intended population, and does its benefit outweigh its harms over the relevant years? The controlled clinical evidence is where the first question begins to receive a firmer answer.

The Controlled Correction

The 2026 study was designed as a double-blind, placebo-controlled pilot in adults aged 60 or older with mild cognitive impairment. Eighty-three people were randomized, 80 started treatment, and follow-up lasted two years. Investigators tested lithium carbonate, not lithium orotate. None of six prespecified coprimary outcomes met the trial's significance threshold. The authors described the result as supporting the feasibility of a larger study, not as establishing efficacy.[4]

A verbal-memory measure favored lithium numerically. In another setting, that might have become the headline. Here it had a nominal *P* value of.05, while the study's prespecified threshold for its multiple primary comparisons was $P<.01$. It therefore did not meet the rule set before the results were known.[4] Prespecification matters most when an outcome looks hopeful: without it, a study that checks several measures can be retold around the most favorable one. Exploratory findings may help shape another trial. They do not retroactively turn a missed primary result into a demonstrated treatment effect.

Neither does the threshold make the observed difference meaningless. A small pilot can leave a clinically interesting possibility unresolved, especially when its purpose includes learning whether a larger study is workable.[4] The disciplined reading is narrower than either "lithium works" or "lithium can never work." The trial tested the question in people under rules stated in advance, and its principal results did not pass those rules. Whether a future study finds a different result remains a future question.

The trial involved people who already had mild cognitive impairment. Its null finding is not a definitive trial of dementia prevention among adults without symptoms. That limit cuts both ways. It prevents a sweeping claim that every lithium hypothesis has been disproved; it also prevents the trial from being used as evidence that lithium prevents decline before symptoms. In the series scale, B-null means a controlled human study did not show an effect on the endpoint it tested. The pilot earns that designation for its tested MCI outcomes. The broader lithium-prevention headline remains C, reflecting observational human associations, not a proven intervention.[4,8,10]

The forum did not simply ignore the correction. On April 19, 2026, RobTuck opened a thread on the trial with the words, "Not wanting to waste anyone's time, I hesitated in posting this. I suspect we will be hearing about it."[11] Its title, "Flawed Study Asks Important Questions on Lithium,"

captured a familiar tension: a disappointing study can be limited and still be important. Questions about sample size, outcome choice, and participants' underlying pathology are legitimate research questions. They do not erase the prespecified miss.[4]

A second response was to separate orotate from carbonate. The Nature-related mouse findings involved lithium orotate; the human pilot tested lithium carbonate.[3,4] Formulations can differ, and a trial of one cannot mechanically be called a trial of another. But the converse does not follow: there is no demonstrated human dementia benefit for orotate that can be preserved by declaring the carbonate result irrelevant. A 2026 chemistry and safety commentary found no evidence yet that lithium orotate remains stable as an intact compound in physiological fluids after oral administration. It discussed dissociation and experimental evidence suggesting that orotate and carbonate may have comparable pharmacokinetics. The commentary was not itself a clinical trial.[7]

This is a common failure mode in supplement reasoning. A distinctive label becomes both an explanation for success in an animal model and an escape from an unfavorable human result, without the bridging human evidence needed for either claim. Lithium orotate may warrant direct study. Until then, "not tested by the pilot" is a statement about the trial's scope, not evidence that orotate works better or is safer. The commentary also warned that unsupervised lithium supplementation can pose risks.[4,7]

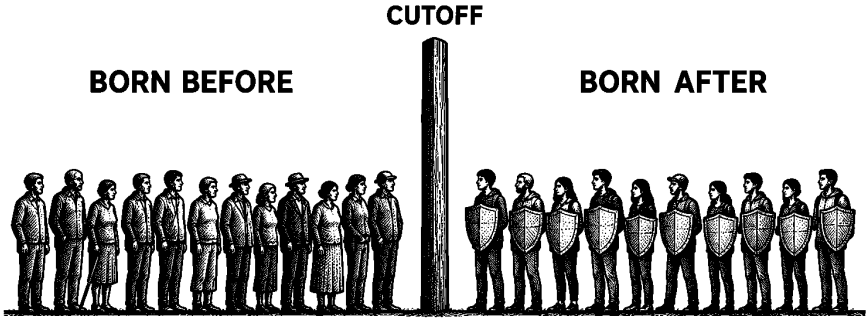


Figure 12. A natural experiment. In Wales, eligibility for the live shingles vaccine depended on date of birth, so people born just before and just after the cutoff were otherwise similar. Comparing their later dementia diagnoses therefore needs fewer assumptions than an ordinary cohort study does.

Seen together, the lithium studies form a hierarchy rather than a vote. Postmortem tissue and mice suggest a mechanism. Cohorts provide mixed human associations, with a favorable pooled estimate and a Scottish study that found no protection at its measured levels. A small controlled MCI trial missed its prespecified outcomes. A meta-analysis published later on the calendar did not include that trial in its randomized synthesis.[3,4,8,10] None of these findings should be hidden; none should be promoted beyond the question it answered. For the fuller distinction between natural experiments and randomized trials, see Book One, *The Longevity Operating System*, Chapter 2, "The Hierarchy of Evidence."

A Vaccine Natural Experiment

Vaccines introduced a different kind of evidence. Ordinary comparisons between vaccinated and unvaccinated adults are hard to interpret because the two groups may differ before anyone receives a shot. People who seek vaccination may also have more contact with health services, different underlying illnesses, or different opportunities to receive a dementia diagnosis. Statistical adjustment can address measured differences, but not every difference is recorded. The Welsh shingles-vaccine study found an unusually informative comparison in a rule people did not choose: eligibility based on date of birth.[5]

Under the Welsh program studied, people born just on one side of the cutoff were eligible for a live-attenuated zoster vaccine, while those born just on the other side were not. Close to that boundary, a few days' difference in birth date sharply changed access: vaccination uptake was 47.2% among those just eligible and 0.01% among those just ineligible. The primary analysis included 282,541 people without dementia at baseline.[5] Neighbors in birth date are less likely to differ systematically in lifelong health behavior than people who independently decide whether to be vaccinated. The cutoff therefore provides a stronger test of the association than an ordinary vaccinated-versus-unvaccinated comparison.

Over seven years, the Welsh analysis estimated that vaccine receipt was associated with a 3.5-percentage-point lower probability of a new dementia diagnosis, equivalent to a 20.0% relative reduction; the reported 95% confidence interval for the relative estimate ran from 6.5% to 33.4%. The estimated effect was stronger among women than men.[5] Both ways of presenting the result matter. A relative reduction can sound immense without the absolute difference; an absolute difference alone can conceal how it compares with the outcome frequency in this particular population. Neither number turns a birth-date natural experiment into a randomized dementia-prevention trial.

The rule's strength also defines its limits. Eligibility did not mean every eligible person was vaccinated. The estimate connecting receipt to dementia diagnoses depends on the assumptions used to translate that large eligibility-driven difference in uptake into a vaccine effect. A cutoff can reduce the usual "healthy vaccinee" problem, but it cannot guarantee that no other policy or recording difference occurred at the same boundary. Nor does a new diagnosis capture every case of disease with identical timing and certainty. Those cautions do not make the Welsh design

ordinary. They explain why it is persuasive observational evidence rather than grade A clinical proof.[5]

An Australian study offered a related, smaller result using age-based eligibility for free live-attenuated zoster vaccination. Its dementia-outcome analysis included 18,402 patients in primary-care records. Eligibility was associated with a 1.8-percentage-point reduction in new dementia diagnoses over 7.4 years, with a 95% confidence interval from 0.4 to 3.3 percentage points. Importantly, this was an estimated effect of eligibility, not of confirmed vaccine receipt.[12] The Australian finding supports attention to the Welsh result while also showing why apparently similar percentages should not be casually lined up: the studies estimated different quantities. An eligibility effect will generally reflect both the policy's change in uptake and whatever effect vaccination itself may have; it is not simply a second measurement of the Welsh per-recipient estimate.

Their product matters as well. Both birth-date studies concerned the older live-attenuated zoster vaccine, not the recombinant shingles vaccine Shingrix.[5,12] It is plausible that preventing shingles or changing an immune response could have effects beyond preventing a painful rash. Plausibility cannot tell us whether two different vaccines produce the same dementia outcome. As of October 2026, CDC recommendations for recombinant zoster vaccination were recommendations for shingles prevention; dementia prevention was not an indication.[13] A claim about an additional benefit must stand on its own evidence, not borrow certainty from a vaccine's established purpose.

A shorter observational comparison addressed recombinant vaccines more directly. In electronic health records for 436,788 people, recipients of an AS01-adjuvanted RSV vaccine and recipients of recombinant shingles vaccine were compared with influenza-vaccine recipients over 18 months. The RSV group had 29% more dementia-diagnosis-free time than the flu-vaccine group; the shingles group had 18% more. Researchers discussed the shared adjuvant as one possible explanation.[14] "More diagnosis-free time" is the reported comparison, not a percentage-point reduction in dementia cases; substituting one for the other would change the meaning of the result. The comparison also does not establish that RSV vaccination prevents dementia, that the adjuvant caused the difference, or that influenza vaccination has no dementia effect.[14]

For RSV and influenza vaccines, the grade is therefore C/Insufficient, claim-dependent. C describes observational human associations where

they exist; Insufficient applies to a specific dementia-prevention claim that the available comparison cannot determine, especially a claim about influenza when influenza vaccination served as the comparator.[14] These grades say nothing against vaccines' established indications. They keep an intriguing additional claim from borrowing certainty from their accepted use against infection.[13,14]

Even natural experiments can produce estimates too large to accept without scrutiny. An August 2026 commentary questioned the very large per-vaccinee reductions implied by a Canadian zoster-vaccine natural experiment, approximately 66%, and as high as 89% under some estimates. Its authors argued that an effect of that size on *all-cause* dementia was difficult to reconcile with a wholly causal interpretation and might be partly inflated by bias. They also noted that, in Wales, declines in shingles and dementia diagnoses occurred concurrently rather than a decline in shingles clearly preceding a decline in dementia.[15] If preventing shingles is the proposed path to preventing later dementia, that timing deserves attention.

The objection is not proof that the vaccine effect is zero. A vaccine might act through more than one pathway, and diagnoses are imperfectly timed measures of the underlying disease. But a mechanism that can explain any timing or any magnitude loses some of its power to test the claim. The best reading as of October 2026 is high-quality C for the shingles-vaccine dementia association: human observational evidence made stronger by birth-date natural experiments, with effect size and generalizability still contested. It is not a randomized result showing that Shingrix prevents dementia.[5,12,14,15]

The Antiviral Trial Closes a Door

The vaccine findings fed a wider question: might persistent or recurring viruses contribute to Alzheimer's disease? Herpes simplex virus is one candidate. A 2025 meta-analysis gathered 26 observational studies involving 1,213,193 participants and found higher Alzheimer's estimates among people with HSV infection. Its pooled cohort hazard ratio was 1.20, while case-control studies produced an odds ratio of 1.32. The authors described the findings as hypothesis-generating and called for research better able to clarify causality.[16]

There are several possible readings of such an association. Infection might contribute to disease in some people. A third factor might affect both the likelihood of recorded infection and the likelihood of an Alzheimer's

diagnosis. Or changes associated with developing disease might alter which infections are noticed and documented. Observational studies alone cannot choose among those accounts.[16] The relative measures require care, too: a cohort hazard ratio and a case-control odds ratio are not interchangeable descriptions of absolute risk. Combining their headline numbers into one simple estimate of "what HSV does" would conceal both the designs and the uncertainty about cause.[16]

An antiviral trial offered a more direct question: if HSV contributes to ongoing decline in early symptomatic Alzheimer's disease, would suppressing it improve the measured clinical outcome? VALAD tested that question under controlled conditions. The phase 2, double-blind trial randomized 120 HSV-seropositive people with early symptomatic Alzheimer's disease to valacyclovir or placebo; 93 completed it. Outcomes were assessed over 78 weeks. On the primary cognitive measure, ADAS-Cog11, the valacyclovir group worsened more, with a between-group difference of 3.93 points in the direction of greater impairment, a 95% confidence interval from 1.03 to 6.83, and P=.01.[6] It was not simply an inconclusive trial that failed to detect a small benefit. Its principal clinical result ran against benefit.[6]

That result earns B-null with a harm signal for valacyclovir in the population and endpoint tested: controlled human evidence found no cognitive benefit in early symptomatic Alzheimer's disease and observed greater worsening on the primary outcome.[6] A trial of 120 randomized people does not settle every possible viral theory. It does close the door on presenting this tested antiviral approach as supported treatment for cognition in that setting. Valacyclovir remains a prescription antiviral with established uses; this Alzheimer's result does not create a cognitive indication.[6]

The boundary matters. VALAD enrolled people who were HSV-seropositive and already had early symptomatic Alzheimer's disease. It did not test whether treating an infection years before symptoms could alter eventual dementia risk, and its result cannot establish that HSV plays no part in disease development.[6,16] But an untested earlier window should not be turned into a recommendation when the tested symptomatic window produced a worse outcome. That would repeat the escape maneuver seen in the lithium debate: each negative test would merely move the claimed benefit to a different formulation, population, or time, without evidence from that new setting.

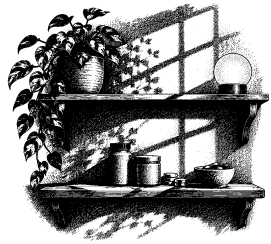
The three reversals in this chapter are not the same verdict. Lithium's brain-tissue and mouse findings remain scientifically interesting, while its controlled MCI pilot missed its clinical targets.[3,4] Shingles-vaccine birth-date studies offer unusually strong observational evidence, while leaving the size of any causal effect and its transfer to recombinant vaccine unresolved.[5,12,15] VALAD directly tested an antiviral in early symptomatic disease and found greater decline rather than relief.[6] The task is to let each result change the claim it actually tested, without demanding that one study answer every adjacent question.

Status as of October 2026

As of October 2026, the March lithium pilot, September lithium meta-analysis, shingles-vaccine correspondence, and VALAD should be checked for later corrections or follow-up before their results are presented as current. The pilot missed its prespecified outcomes; the meta-analysis's randomized synthesis did not include it.[4,6,10,15]

As of October 2026, vaccine recommendations should be checked separately from dementia claims. The cited shingles-vaccine recommendation concerns shingles prevention, not an established dementia-prevention indication.[13]

Chapter 18: Light, Sound, and the Supplement Shelf



“Very interesting. Dr Fontana actually says at end of video that this is something humans could do now…” Neo wrote in a March 12, 2024, forum thread about a Nature paper on 40 Hz sensory stimulation and amyloid clearance.[1] The thought was understandable: if a pattern of light and sound helped clear a protein associated with Alzheimer’s disease in mice, perhaps people would not have to wait for a new drug. Another member, medaura, pressed on a detail that hope could easily flatten: were the sounds people could find online even the same stimulus the animals had received?[2]

That question reaches beyond the distinction between one sound and another. The mouse work concerned a proposed clearance mechanism; a person considering dementia prevention wants to know whether an intervention preserves memory and functioning over years. Between those claims lie changes in species, device, population, endpoint, and time. By October 2026, human studies of sensory stimulation had made the discussion more substantial than it was in that March thread. They had not carried the mouse finding all the way to a prevention result.

The same distance appears, in different forms, along the supplement shelf. Omega-3 can reach the central nervous system without changing measured cognition. B vitamins can slow an MRI measure of atrophy in a trial subgroup without establishing that fewer people develop dementia. A multivitamin can produce a small cognitive-test advantage while a neighboring cocoa-flavanol result is null. None of those distinctions makes the forum’s interest foolish. They make the precise claim worth protecting from a more attractive, less accurate one.

A Rhythm Reaches Humans

In the preclinical account that caught the forum's attention, patterned sensory stimulation was associated with amyloid clearance. That is a finding about a proposed biological route, not a demonstration that a human brain will clear amyloid in the same way, much less that a person without symptoms will avoid dementia. The distinction also applies to the stimulus itself. In the March thread, medaura observed that binaural beats and the sound used in the animal study were not necessarily equivalent; Olafurpall later put the point plainly: "40 Hz can mean different things."[2,3]

Human research has since moved past speculation, but it has not resolved the largest question. OVERTURE, a sham-controlled study of 76 people with Alzheimer's disease over six months, provides the small human treatment signal behind this chapter's B grade: a controlled signal with limits, in people already symptomatic. The sponsor has identified EEG biomarkers from OVERTURE as supportive mechanistic evidence for the larger HOPE trial, but has not reported a quantified clinical outcome that would establish the size or reliability of a treatment benefit. OVERTURE cannot show that 40 Hz stimulation prevents Alzheimer's disease.[4]

EEG evidence matters because an intervention should at least engage something plausibly related to its proposed mechanism. It is not an answer to the clinical question. A measured change in brain activity does not tell us whether a patient will retain the ability to manage ordinary tasks, whether any difference persists, or whether it outweighs the demands of using a device. Exploratory findings can narrow a hypothesis while leaving the outcome that families care about unresolved.

A smaller Phase 2 study called FLICKER illustrates the temptation to keep moving from one plausible link to the next. A July 2026 sponsor report described changes in several cerebrospinal-fluid proteins involved in lipid transport among ten amyloid-positive participants with mild cognitive impairment. The release itself treated these findings as exploratory and called for evaluation in adequately powered trials. Protein changes do not establish clinical improvement, and ten participants cannot settle whether the pattern will recur.[5]

HOPE is designed to ask a larger treatment question. Its registry describes a randomized, double-blind, sham-controlled study of about 670 people with mild to moderate Alzheimer's disease, with a primary measure combining cognition and daily functioning. As of October 2026, the registry listed the study as completed, with primary completion on June 22,

2026, and study completion on August 17. As of October 10, neither a topline efficacy result on the registry nor a company announcement of one had been located. Completion is an event in a trial's calendar, not a favorable result. Nor does a study's appearance in a federal device registry establish marketing approval.[6]

The resulting grade has two parts and should not be shortened to one. 40 Hz gamma stimulation is B for a small treatment signal, where B means controlled human evidence with important limits. It is Insufficient for prevention: the available studies do not establish a benefit for at-risk adults without dementia. HOPE may strengthen, weaken, or complicate the treatment case when its results appear, but it studies symptomatic disease rather than primary prevention.[4,6]

That distinction is easy to lose when the proposed intervention looks less invasive than a drug. A commercial description can move quickly from an animal clearance mechanism to human brain-activity measurements, then to a small treatment study, and finally to language that sounds like protection for any older customer. Each step changes the claim. Greater confidence in those earlier findings cannot substitute for a prevention study.

Light Through a Smaller Trial

Transcranial photobiomodulation, or tPBM, belongs beside sensory stimulation in a discussion of devices, but not in the same evidence file. It uses light in a different intervention, tested with different methods and outcomes. A forum thread begun in July 2024 brought several kinds of proposed brain-directed devices into one conversation. Its title promised devices that would reverse Alzheimer's cognitive decline and increase longevity; within the thread, members questioned presentations, discussed published papers, and distinguished possible cognitive effects from proof.[7,8] The grouping shows how readily "non-drug" becomes a category of apparent similarity. A result for one device cannot validate the others.

In April 2026, researchers published a randomized, double-blind, placebo-controlled home tPBM trial involving 80 people with mild cognitive impairment due to Alzheimer's disease. At week 13, the mean Korean MoCA score had risen 3.87 points in the active group and fallen 0.74 points in the placebo group; other reported cognitive scales also favored active treatment. The authors reported no device-related adverse

events and high adherence during the short trial. These are encouraging controlled findings, not merely before-and-after testimonials.[9]

The design deserves credit precisely because it sets a boundary around the result. The participants already had MCI attributed to Alzheimer's disease; they were not an unscreened population seeking prevention. The trial measured cognitive tests over weeks, not conversion to dementia over years. Its size leaves questions about replication, the stability of the effect, and how well the finding carries beyond the studied population and device. An absence of reported device-related adverse events in 80 participants over that period does not establish the safety profile of every product sold with a cognition claim.[9]

A July 2026 network meta-analysis offered a wider view, combining 35 randomized trials from 34 studies and 1,559 participants across photobiomodulation and other forms of brain stimulation. Its estimates favored photobiomodulation over control on two cognitive scales. Yet most comparisons between active interventions were indirect, and the photobiomodulation studies differed in wavelength, treatment course, and other features. An indirect ranking can make an intervention look settled even when there has been no decisive head-to-head test of the specific products a reader might encounter. The pooled estimate is not the measured effect of one device.[10]

That is why the headline grade for transcranial photobiomodulation is C for preventing dementia or slowing cognitive decline in at-risk adults without dementia. C denotes evidence short of a controlled result for that headline claim; it does not erase the narrower controlled cognitive signal in one MCI trial. Calling the device simply "proven" would conceal the population and duration. Calling the trial meaningless would discard a useful reason for larger, independent studies.[9,10]

The two device stories have different evidentiary shapes. For 40 Hz stimulation, a larger symptomatic-treatment trial has finished but had not reported its primary outcome as of the chapter's date. For tPBM, a striking short trial has reported, while replication and longer outcomes remain open. In neither case can a mechanism, a cognitive scale, and a prevention claim be treated as interchangeable currencies.[6,9]

Omega-3 and a Target-Engaged Null

The supplement shelf offers a sterner example because omega-3 fatty acids arrived with a long-standing biological rationale. DHA is a component of brain tissue; observational associations and dietary arguments make the idea appealing. But supplementation must be judged by what assigned groups actually experienced, not by how plausible a nutrient's role sounds. The strongest test of a prevention-oriented cognitive claim is not whether people who eat differently also differ in dementia risk. It is whether adding the supplement changes outcomes under controlled conditions.

A 2024 systematic review pooled 24 placebo-controlled trials involving 9,660 people aged 40 or older without dementia. Across interventions lasting three to 36 months, the pooled global-cognition result was not statistically significant: a standardized mean difference of 0.041, with a confidence interval spanning no effect. Exploratory dose-response analyses suggested a possible executive-function benefit in some settings, but did not demonstrate dementia prevention. That narrower possibility is a reason to investigate a specified population and outcome, not to relabel the overall result positive.[11]

Evidence in established Alzheimer's disease has also resisted an easy positive reading. A Cochrane review of three trials involving 632 people found no clear six-month benefit on ADAS-Cog, daily functioning, dementia severity, or quality of life. A later synthesis of placebo-controlled Alzheimer's trials likewise found no statistically significant pooled ADAS-Cog benefit. These treatment findings do not by themselves answer every prevention question, but they weaken the notion of a broadly dependable cognitive effect.[12,13]

Then came a more pointed test of one possible explanation for earlier failures: perhaps supplements had not delivered enough DHA to the central nervous system. A 2026 randomized trial enrolled 365 adults aged 55 to 80 without dementia, with low dietary DHA intake and at least one dementia risk factor. It found that the tested DHA regimen increased the cerebrospinal-fluid DHA-to-arachidonic-acid ratio at six months, without evidence that this biochemical response differed by APOE ε4 status. Over 24 months, however, cognition and brain volumes did not differ between treatment and placebo groups. Attrition was substantial, 38 percent, mainly during the COVID-19 period, and limits confidence about smaller effects. It does not turn the observed null into a benefit.[14]

This is a *target-engaged null*: the measured biochemical target moved, while the measured clinical and structural outcomes did not. It rules out the simplest claim that nothing happened because DHA never reached a relevant compartment. It cannot rule out every effect in every subgroup or over a longer period. Conversely, invoking a possible longer period cannot convert an unobserved effect into an observed one. Trials have finite power and duration; readers should know those limits without having to set aside their results.

The forum argued over exactly that tension. In March 2025, Rapan questioned whether a trial of this size and duration could detect the desired cognitive effect; adssx replied that it was large compared with many trials the forum discussed.[15,16] Both concerns can coexist. A null trial may leave a small or delayed effect uncertain, while still being stronger evidence than an attractive mechanism or an uncontrolled report. Uncertainty about what was missed is not evidence that the missed effect exists.

For the cognitive claim tested, omega-3 receives B-null: controlled human evidence has not shown a benefit on the relevant endpoints across the cited trials and syntheses. “Null” is attached to those endpoints, populations, and follow-up periods, not to every reason a person might eat fish or every possible biological role of fatty acids. That disciplined scope matters as much for a negative grade as for a positive one.[11,13,14]

One proposal tries to rescue the omega-3 story by placing B vitamins beside it. It deserves its own examination rather than an assumption that two plausible ingredients make a demonstrated program. VITACOG randomized 271 people older than 70 with mild cognitive impairment to B vitamins or placebo for 24 months. In the MRI subset, annual whole-brain atrophy averaged 0.76 percent with B vitamins versus 1.08 percent with placebo. Participants whose baseline homocysteine exceeded 13 micromoles per liter showed a larger difference in atrophy rates. The study did not establish fewer conversions to dementia.[17]

The high-homocysteine result makes biological and research sense as a subgroup question: a treatment aimed at lowering homocysteine might have more room to show an effect where the baseline measure is higher. Yet subgroup findings can also be unstable. A result in an MRI subset is not automatically a population-wide clinical outcome, and slower measured atrophy is not identical to preserved independent functioning. Proposed interactions with omega-3 add another layer that would require a direct, adequately powered test of the combined claim. Studies of omega-3 and B

vitamins have not shown that combining them prevents cognitive decline or dementia.[11,17,18]

A 2025 review of 17 randomized B-vitamin trials involving 5,275 older adults found a possible global-cognition benefit, but rated its in general, highly heterogeneous estimate very low certainty. After excluding statistical outliers and single-blinded studies, the estimated benefit was small, at 0.110 standard-deviation units. The review did not find a significant difference in effect by whether participants began with intact cognition, MCI, or dementia. It therefore offers some support for a small cognitive effect without validating a universal high-homocysteine prevention strategy.[18]

The grade is C/B for B vitamins in high-homocysteine subgroups, narrowly qualified. The B recognizes controlled human signals, particularly VITACOG's atrophy finding; the C headline reflects how far a subgroup and surrogate outcome remain from established dementia prevention. It is not a verdict against correcting a documented nutritional problem for its own reasons. It is a refusal to treat an interesting interaction proposal as an established combination intervention.[17,18]

The Rest of the Shelf

The rest of the shelf does not yield a single answer. In COSMOS, a pooled analysis of three nonoverlapping cognitive substudies found a 0.07-standard-deviation advantage in global cognition and a 0.06-standard-deviation advantage in episodic memory for multivitamin-mineral supplementation. The authors compared the global-cognition difference to about two years of cognitive aging. That comparison translates a test-score difference into a familiar scale; it is not a finding that dementia began two years later, or that fewer participants developed it. Nor were the three substudies independent replications from unrelated research programs: they belonged to the same parent trial.[19]

The multivitamin therefore earns B for small cognitive gains, a controlled human signal with limits, and Insufficient for dementia prevention. Both clauses matter. A small mean test-score advantage can be real without being large enough, durable enough, or directly tied enough to a later diagnosis to establish the prevention claim. The point is not that every small effect is worthless. It is that a modest measured difference should retain its original units when it reaches the public.[19]

Cocoa flavanols, also examined within COSMOS research, tell a different story. In COSMOS-Web, 3,562 older adults were assigned cocoa extract or placebo for three years. The prespecified year-one memory endpoint across all participants was not statistically significant. Results favored flavanols among participants with lower baseline diet quality or habitual flavanol intake, a finding that could reflect a real deficiency-related effect or the instability of subgroup comparisons. It does not reverse the primary result for the full trial population. Cocoa flavanols receive B-null on the primary claim: the controlled test did not show the proposed overall memory benefit.[20]

Vitamin D requires an especially clean separation between two questions. Deficiency can matter for health in its own right; that does not establish that adding vitamin D prevents dementia in a population largely sufficient at baseline. In a Finnish randomized trial of 2,492 dementia-free adults followed for a mean of 4.2 years, neither tested vitamin D regimen significantly changed diagnosed dementia incidence. The number of diagnoses was modest, so the trial has limited ability to exclude a small effect, but its observed result was not positive. Vitamin D is B-null in replete adults for the dementia-prevention claim tested.[21]

VITAL supplies a separate, narrower piece of evidence, sometimes mistaken for a dementia-outcome result. A 2026 secondary analysis measured four plasma biomarkers associated with Alzheimer's disease and related dementias in 929 participants over four years. Vitamin D did not significantly change those biomarkers overall; neither did omega-3. Reported sex and race subgroup signals were not adjusted for multiple comparisons and were identified as hypothesis-generating. The Finnish trial addresses diagnosed dementia; this VITAL analysis addresses biomarkers. They should not be merged into a claim that VITAL proved a dementia-incidence effect in either direction.[21,22]

Other familiar products sit still farther from a controlled cognitive benefit. A 2025 creatine pilot followed 20 adults with Alzheimer's disease without a randomized comparison group. Brain total creatine rose 11 percent and cognitive composites improved from baseline. Without a control group, those changes cannot separate a treatment effect from practice, expectation, selection, or ordinary variation. The pilot is evidence that the proposed biological target can move under study conditions, not that creatine treats Alzheimer's disease.[23]

The recurring difficulty is not confined to one nutrient. A product may have an appealing role in metabolism, a measurable effect in blood or brain, or a small test-score change, while the claim on its label or in conversation concerns years of independence. The gap has to be stated each time because the studies differ: omega-3 has target engagement alongside null cognitive findings; the multivitamin has a small cognitive signal without a dementia endpoint; cocoa has a null primary memory result; vitamin D has a null diagnosed-dementia result in a largely sufficient trial population. Flattening all four into "supplements work" or "supplements do nothing" loses the useful evidence.[14,19,20,21]

For general supplement appraisal, see *The Longevity Operating System*, Chapter 13. The question here is narrower: whether a memory-protection claim survives contact with the population, comparison group, duration, and endpoint that produced the cited result.

Claims and Enforcement

The distance between a research result and a retail claim becomes harder to see when the product itself is uncertain. A 2025 surveillance study by 12 official medicines-control laboratories examined 159 samples collected in Europe and Australia from January 2020 through September 2024. About 49 percent were sold or presented as dietary supplements, and 69 percent came from the illegal market. Testing identified prescription drugs and unauthorized substances, including compounds sold under the broad appeal of "nootropics." Those percentages describe the collected samples, not the prevalence of adulteration across every supplement sold to consumers.[24]

That distinction does not make the finding trivial. A cognitive claim can fail at two levels: the advertised ingredient may not have demonstrated the promised benefit, and a product presented as a supplement may contain a different pharmacologically active substance. Evidence about an ingredient cannot establish the contents of an untested product. Nor does a product's legal classification as a supplement validate a claim that it prevents dementia.

Regulatory findings need to be distinguished from clinical evidence. FDA regulatory status addresses whether a product is approved for a particular use; an FTC action, if one is identified, addresses specific marketing claims. The nootropic-surveillance study documents a safety concern about product contents, not an FTC finding about a memory advertisement.[24]

Clinical efficacy, product contents, lawful marketing, and an agency's finding about a specified advertisement are four different questions.

For checking product claims against their underlying sources, see *The Longevity Operating System*, Source Appraisal Handbook.

The forum's attraction to devices makes sense in this setting. Light and sound seem to escape the uncertainties of a bottle's contents; a multivitamin looks familiar beside unfamiliar nootropics. Familiarity and novelty, however, are poor substitutes for a claim stated at the scale of its evidence. The strongest current device studies concern people already experiencing MCI or Alzheimer's disease. On the shelf, the clearest controlled supplement results range from small cognitive gains to null primary outcomes. For prevention, the most honest description often remains an open question rather than a product promise.[6,9,11,19,20,21]

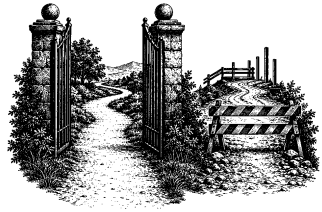
Status as of October 2026

As of October 10, 2026, HOPE was listed as completed, but no topline efficacy result had been posted on its trial registry or announced by the company. Trial completion alone does not establish a positive outcome.[4,6]

As of October 10, 2026, the nootropic-surveillance study documented a product-safety concern, not an FTC action about memory claims. Findings about what products contain should not be mistaken for findings about whether a particular advertisement broke the law.[24]

Part V: What Holds Up

Chapter 19: The Antibodies Arrive



On December 12, 2025, RapAdmin opened a forum discussion around a longevity-summit presentation on dementia. The accompanying research digest began with a familiar account: “For nearly three decades, the ‘Amyloid Cascade Hypothesis’ has dominated research.”[1] The discussion was about possible advances, but it also exposed a distinction this book has deferred. A drug can slow decline after Alzheimer’s symptoms begin without having shown that it prevents symptoms from beginning.

That distinction matters because the first part is no longer hypothetical. In controlled trials, two antibodies directed against amyloid slowed measured decline in people who already had mild cognitive impairment or mild dementia due to Alzheimer’s disease. The differences were real, though modest on the trials’ scales. The participants had been selected for evidence of Alzheimer’s pathology, and treatment brought substantial risks and monitoring demands. Neither trial tested routine use in people who felt well and wanted to remain that way.[2,3]

A person reading about these drugs may reasonably feel both relief and impatience. After years of failed Alzheimer’s trials, a measurable clinical effect is an achievement. Someone with a diagnosis may hear that news very differently from someone looking for a prevention strategy. Yet the two questions cannot be collapsed without changing the evidence. Slowing an established illness is a treatment claim. Preventing that illness is another claim, in another population, requiring another trial.

The Symptomatic Outcome

CLARITY AD enrolled 1,795 people with mild cognitive impairment or mild dementia due to Alzheimer's disease and confirmed amyloid. Over 18 months, the Clinical Dementia Rating–Sum of Boxes score, or CDR-SB, worsened by 1.21 points in the lecanemab group and 1.66 points in the placebo group. The between-group difference was 0.45 points, commonly described as about 27 percent slower decline on that measure. These are group averages, not a prediction of what any one family will notice. Both groups worsened.[2]

The relative figure can sound larger than the absolute difference because it answers a different question: how much smaller was the treatment group's average worsening compared with the placebo group's? It does not mean that 27 percent of patients avoided dementia, or that a patient retained 27 percent more of every ability. The 0.45-point difference anchors the claim to the scale and observation period actually studied.[2] Neither number, alone, describes what an individual household experienced.

TRAILBLAZER-ALZ 2 enrolled 1,736 people with early symptomatic Alzheimer's disease and evidence of amyloid and tau pathology. In its low- and medium-tau group, CDR-SB worsened by 1.20 points with donanemab and 1.88 with placebo over 76 weeks, a difference of 0.67 points. The trial reported statistically significant results on 23 of 24 outcomes in its prespecified testing sequence. That wider pattern supports the conclusion that the finding was not an isolated favorable score, while the population and duration still define what the result can establish.[3]

The 0.45- and 0.67-point differences should not be arranged into a league table. They came from separate trials with different enrolled populations and observation periods; the donanemab figure above concerns a specified tau subgroup.[2,3] Choosing one antibody over another by comparing those two numbers would treat unlike comparisons as though they were a head-to-head experiment. It would also leave out the safety and eligibility questions that accompany either treatment.

These results support this chapter's A grade for slowing decline in studied early symptomatic Alzheimer's disease: clinical outcomes in relevant controlled trials. The grade belongs to that narrow treatment claim, not to amyloid removal in general and not to use before symptoms. For prevention, the grade remains Insufficient. Trials in people without cognitive impairment must answer whether treatment delays clinical

disease enough to justify exposing otherwise well participants to its burdens and risks.[2,3,4]

“A” also needs to be read alongside the size and meaning of the outcome. CDR-SB combines assessments of cognition and everyday function; a difference in its average rate of worsening does not mean that treatment restores lost abilities. It does not tell a household precisely how much more independent a particular person will be at a particular date. The trials provide evidence that decline was slowed across their studied groups. The decision that follows in clinical practice involves a different sort of uncertainty: whether that average benefit is worthwhile for an eligible person facing a known set of hazards.

Amyloid clearance strengthens the biological account of what the antibodies do, but it is not interchangeable with the clinical result. A treatment can change a scan and still fail to make a meaningful difference in how people think or function. Conversely, a clinical effect need not settle every dispute about the mechanism of Alzheimer’s disease. The antibody trials show that intervening against amyloid can alter the course measured in selected symptomatic patients. They do not establish that amyloid is the only useful target, that earlier intervention must work better, or that every method of lowering amyloid has the same effect.[2,3]

Selection in the trials was not an administrative footnote. The enrolled patients had early symptoms and evidence of the pathology the drugs target.[2,3] A person with memory complaints from another cause would not become an appropriate candidate simply because a new Alzheimer’s medicine exists. Nor can the result be transported unchanged to people with more advanced dementia, people outside the trials’ safety criteria, or asymptomatic adults concerned about family history. The further the proposed use moves from the studied population, the less work the A grade can do.

The controlled comparison also guards against a misleading story sometimes told about dementia care: that any period of stability proves a treatment worked. Alzheimer’s symptoms and test scores vary, and individual trajectories are uneven. In these trials, the placebo groups made it possible to estimate a difference attributable to treatment rather than to the ordinary variation visible in any clinic.[2,3] That is the achievement. Its boundary is just as much a part of the finding.

Eligibility, ARIA, and Monitoring

The clinical benefit came with a characteristic safety problem: amyloid-related imaging abnormalities, known as ARIA. ARIA-E refers to edema or effusion; ARIA-H includes microhemorrhages and superficial siderosis. Some abnormalities are found on surveillance imaging without obvious symptoms. Others can be symptomatic, serious, or fatal. The labels for these medicines carry boxed ARIA warnings.[5,6]

In CLARITY AD, ARIA with edema occurred in 12.6 percent of lecanemab recipients and 1.7 percent of placebo recipients, an absolute difference of 10.9 percentage points. In TRAILBLAZER-ALZ 2, the corresponding figures were 24.0 percent with donanemab and 2.1 percent with placebo, an absolute difference of 21.9 points; the donanemab trial also reported three treatment-related deaths.[2,3] Those numbers describe events under particular trial conditions. They neither make the risk uniform across patients nor allow a simple comparison of the two drugs, because the studies selected and monitored participants differently.

An ARIA percentage also requires care in interpretation. It counts an imaging-defined event, not necessarily a lasting injury or a symptom the patient felt. But the presence of asymptomatic findings does not make the serious end of the risk distribution irrelevant. The trials' average benefits and adverse-event rates appear in adjacent columns in a paper; for an individual, they may be experienced very unevenly. One person might have no discernible benefit and an imaging abnormality. Another might experience meaningful stability without ARIA. Group data cannot identify either outcome in advance.

APOE ε4 status is one reason the risk is not uniform. A 2026 review summarized a genotype gradient across central antibody trials: reported ARIA-E incidence ranged from 5.4 to 14.8 percent in noncarriers, 10.9 to 23.8 percent in heterozygotes, and 32.6 to 41.1 percent in homozygotes. Those ranges pool findings from different trial settings; they are not an individual risk calculator. The review also identified baseline evidence of cerebral amyloid angiopathy and treatment-related factors as risk considerations.[5]

As of October 2026, the U.S. Kisunla label has a boxed warning that ARIA can be fatal, notes higher risk in APOE ε4 homozygotes, and calls for APOE testing before treatment begins. The lecanemab label likewise warns about ARIA and advises APOE testing before starting. A genotype result can therefore change the risk conversation without turning genetics into a

verdict about whether a person will benefit. The drugs are approved for early symptomatic disease with the required evidence of amyloid, not for people without symptoms.[6,7,8]

Imaging is part of treatment, not an optional confirmation that comes after the important decision. Label-based assessment before treatment and surveillance during it seek to detect ARIA, including abnormalities a patient may not feel. Clinicians also have to distinguish a new neurological symptom from other urgent problems rather than assume it is an expected nuisance. The exact monitoring requirements belong to the current product label and treating service; they should not be reconstructed from a forum account or an older news article.[6,7]

This makes access more complicated than having an approved medicine and a prescription. It calls for diagnostic evaluation, amyloid confirmation, review of relevant risks, capacity for appropriate imaging and follow-up, and a service able to respond to complications. Someone can meet the broad description "early Alzheimer's" yet still face a difficult eligibility or safety decision. Exclusion from treatment is not proof that their symptoms matter less; it reflects the fact that an average trial benefit cannot erase a particular hazard.

Insurance adds another gate. As of October 2026, Medicare's national coverage determination provides coverage for FDA-approved anti-amyloid antibodies through coverage with evidence development, requiring enrollment in a CMS-approved registry or trial under its rules. Coverage is therefore not synonymous with unrestricted availability, and the terms should be checked against the current CMS policy rather than inferred from approval alone. The CMS national registry lists a primary completion date in 2028.[9]

For preparing eligibility and risk questions rather than treating a forum discussion as a consent visit, see *The Longevity Operating System*, Clinician Conversation Handbook.

The resulting tradeoff is uncomfortable precisely because the medicines work on the endpoint tested. If their trials had been entirely negative, the safety discussion would be simpler. Instead, an eligible person and a clinical team must weigh a measured slowing of decline against a risk that can be severe, the possibility that no noticeable individual benefit will emerge, and the practical load of evaluation and monitoring. There is no honest way to turn that into a universal yes or no. The book's role is to keep

the evidence and its limits visible, not to make the choice on behalf of a patient.

The genotype gradient illustrates another limit to easy summaries. A headline trial result averages across people with different susceptibility to ARIA. It cannot tell an APOE ε4 homozygote that the overall adverse-event percentage describes their own risk. Nor does a lower-risk genotype make ARIA disappear. Genetic information may inform a treatment decision made after symptoms and pathology are established; it is not, by itself, a reason for an asymptomatic reader to seek an antibody.

A Changing Delivery Label

The story of lecanemab did not stop at its original presentation. As of October 2026, Leqembi IQLIK, a subcutaneous lecanemab autoinjector, is U.S.-approved for starting treatment as well as for maintenance in the labeled early symptomatic population. The initiation approval was announced on July 14, 2026; the companies planned U.S. Availability beginning in late August. It is a change in the approved delivery options for eligible patients, not an approval for prevention in people without symptoms.[7]

That distinction is easy to miss in an announcement about convenience. A different way of delivering a medicine may change aspects of the treatment experience, but it does not widen the disease stage for which efficacy has been demonstrated. The controlled clinical result remains the symptomatic CLARITY AD result, with the attendant limits of its population. Approval of an additional presentation also does not make the boxed warning, amyloid-confirmation requirement, or monitoring problem evaporate.[2,7]

A practical improvement can be valuable without being a clinical-outcome breakthrough. Less dependence on one form of administration might ease part of the burden for some eligible patients. It would not eliminate the need for a service that can assess risk and detect complications. The more convenient a treatment appears, the easier it becomes to overlook those less visible demands. Delivery and eligibility are separate questions, even when they meet in the same appointment.

The company's July 2026 announcement said that ARIA-E with subcutaneous treatment was expected to be comparable to the intravenous experience, based on modeling from the CLARITY AD open-label extension. "Expected" and "based on modeling" deserve to stay in that

sentence. They are not a new randomized clinical comparison showing that a change of presentation removes the major safety risk. Current labeling, rather than a promotional account of convenience, defines the authorized use and warnings.[7]

Donanemab's label has changed too. A July 2025 U.S. Revision reflected a modified titration approach introduced to reduce early ARIA-E; the company reported a 24-week ARIA-E rate of 14 percent in the study informing that change, versus 24 percent with the earlier approach. That is useful safety information, not a reason to treat ARIA as solved or to substitute a press-release figure for the warning and monitoring language in the current label. This chapter gives no administration instructions: the point is how evolving labels can alter a clinical risk assessment, not how to deliver either drug.[6,8]

Regulatory differences also matter. As of October 2026, the European authorization for donanemab excludes APOE ε4 homozygotes, whereas the U.S. Label emphasizes their higher ARIA risk and APOE testing. "Approved" is therefore incomplete without a jurisdiction, a population, and a date. A news item written at approval may remain accurate about the event that happened while being incomplete about the label now in force.[6,8]

The delivery news presents an editorial trap for a book about prevention. A reader may see a less clinic-centered presentation and imagine treatment shifting gradually into routine use among worried, symptom-free adults. That is a hypothesis about future practice, not a consequence of the 2026 approval. Any such move would need clinical outcome evidence in that different population, an acceptable safety balance, and an applicable authorization. The ease of administering a drug cannot answer whether the person should receive it.

Shuttles and a Crowded Pipeline

If the approved antibodies are a measured advance, the development pipeline is a store of unanswered questions. A review published in 2026 counted, in its January 1, 2026 snapshot, 192 Alzheimer's drug trials assessing 158 drugs, including 54 Phase 3 trials. These figures describe development activity at a date, not 158 promising outcomes. A crowded pipeline can mean substantial scientific effort while still producing many failed tests.[10]

The forum conversation around the dementia presentation showed how quickly an unfamiliar target can become a candidate for everyday discussion. On December 12, 2025, medaura wrote, “Interesting notes but I can’t stomach the big block of AI digest.”[11] The objection was to the form of the material, not a clinical trial verdict. It nevertheless points to a problem with long compilations of mechanisms and early findings: a reader can finish with a powerful sense that something has been established while losing track of which claims rest on patient outcomes. On February 1, 2026, drgathard offered a narrower caution about a compound discussed in that thread: “There doesn’t seem to any strong evidence that Pectasol actually lowers galectin-3 in humans.”[12] Neither forum observation decides the antibody question. Both show why a promising target must be kept separate from a demonstrated effect in people.

Trontinemab is among the candidates attracting attention. Its proposed “brain shuttle” design is meant to address a persistent problem for antibodies: reaching the brain effectively. At an Alzheimer’s conference in 2026, Roche presented or previewed open-label extension findings on amyloid removal, biomarkers, and longer-term safety, while reporting that its Phase 3 TRONTIER 1 and 2 trials in early symptomatic disease were ongoing. Those later trials, not the appeal of the design, must establish whether patients experience clinical benefit.[13]

One reported open-label finding was striking: in a particular trontinemab study group, 92 percent were below an amyloid-positivity threshold at 28 weeks. That is a biomarker observation in an uncontrolled extension, not evidence that 92 percent avoided dementia or improved cognitively. People who remain in an extension can differ from those who do not, and a scan threshold is not a measure of everyday functioning. The chapter’s grade for trontinemab and other pipeline antibodies is Insufficient for a clinical outcome claim. The amyloid finding can inform the rationale for Phase 3 testing; it cannot replace that test.[13,14]

There is a recurring pattern here. A new antibody may clear plaque faster, reach a different compartment, or use a different delivery system. Each proposition can be worth investigating. None automatically settles the two hardest questions: whether a controlled trial shows a worthwhile difference in cognition or function, and whether the benefit outweighs harms in the people proposed for treatment. With prevention, the bar is harder still, because those being exposed have not yet developed the symptoms the existing drugs were studied to slow.

A full pipeline also contains disappointments that deserve a plain account. The European Medicines Agency reported that its committee recommended refusing authorization for blarcamesine in December 2025. The company withdrew its application in March 2026 before re-examination was complete. In the main study, 462 adults with early Alzheimer's disease were assessed over 48 weeks; the agency concluded that effectiveness had not been demonstrated on the two principal measures and raised concerns about analysis methods, limited safety data, and discontinuations. Blarcamesine is graded Insufficient. The cited European regulatory record does not establish its authorization status in every other jurisdiction. An application and a dispute over interpretation are not substitutes for a favorable regulatory finding.[15]

A refusal does not prove that every possible biological idea behind a drug is false. It does mean that the submitted evidence did not support the requested authorization. That distinction cuts both ways: advocates should not present a withdrawn application as a near-approval, and skeptics need not pretend that an agency decision answers every research question. For readers deciding how much weight to place on pipeline headlines, the immediate point is more modest. Development status is not an efficacy grade.

The antibody results have sometimes encouraged a broader claim that Alzheimer's drug development has finally become predictable. The 2026 trial count is a reason for interest, not confidence in any particular candidate. A biomarker can help investigators choose participants or show that a medicine reached its target. A later trial can still find too little clinical benefit, unacceptable harm, or a benefit confined to a narrower group than anticipated. Those are ordinary possibilities in drug development, even after a persuasive early scan.

The Prevention Trials

The strongest reason not to borrow the symptomatic A grade for prevention is that prevention has already produced a major negative test. The A4 trial enrolled 1,169 cognitively unimpaired adults, whose mean age was 72, with elevated brain amyloid. Over 240 weeks, solanezumab did not slow decline on its cognitive composite: the measured change was −1.43 in the treatment group and −1.13 with placebo, a difference that was not statistically significant. Solanezumab also did not substantially clear plaque.[4]

A4 did not test lecanemab, donanemab, or trontinemab. Its null result cannot settle their prevention trials in advance. Solanezumab binds soluble amyloid and differs from the plaque-clearing antibodies now in use or development. But A4 did test a serious version of a once-compelling proposition: identify amyloid before cognitive impairment and treat early enough to preserve cognition. The result is a warning against treating that proposition as established simply because it sounds biologically orderly.[4]

The two readings of A4 are worth holding together. Because solanezumab did not substantially clear plaque, the trial does not show that substantial plaque removal before symptoms fails. Because its clinical result was null, it also cannot be counted as support for prevention.[4] Explaining why one drug may have failed is a reasonable starting point for another trial. It is not evidence that the next drug succeeds.

Prevention trials also have an unusually difficult clock. Participants may be cognitively unimpaired at entry even when biomarkers suggest elevated risk. Some will progress during observation; others will not, regardless of treatment. A study looking for a difference in clinical progression needs enough events to distinguish a drug effect from the slower, less predictable course of disease in that population. An estimated completion year is not the same thing as an observed result, particularly when the number of events helps determine when analysis is possible.

Several programs are intended to answer parts of the prevention question, but their populations and endpoints should not be lumped together. AHEAD 3-45 concerns lecanemab in people without cognitive impairment selected using amyloid-related criteria; as of October 2026, no efficacy result or dependable trial-specific readout date was available. TRAILBLAZER-ALZ 3 is the preclinical donanemab study: a January 2026 pipeline review said a 2026 readout was possible if enough events accrued, not that an outcome was available. A projected date is not a result.[7,10]

Roche has also announced a planned Phase 3 program called PrevenTRON in cognitively unimpaired people at high risk of progression. Its announcement described using a blood-based p-tau217 test to help find potential participants; it did not report prevention efficacy. Trial recruitment tools should not be confused with a general screening invitation. As of October 2026, no Alzheimer's blood test is cleared in the United States to screen people without symptoms. The existence of a research enrollment strategy does not change that regulatory boundary.[13,14,16,17]

A biomarker-selected study population is also not everyone who worries about dementia. Selection can make a trial better able to detect an effect by concentrating people thought to be at higher risk. It can simultaneously narrow the group to whom a positive finding would apply. Even if a future study succeeds, its entry criteria will matter: an outcome among selected participants cannot automatically be assigned to all asymptomatic adults, including those whose concern rests only on age or family experience.

Other trial names create another hazard for readers of fast-moving coverage. A published abstract describes TRAILRUNNER-ALZ 3, a Phase 3 remternetug study including preclinical Alzheimer's disease and mild cognitive impairment, with time to clinical progression as its primary endpoint. The abstract gives information about the study and its enrolled groups, not a treatment-efficacy finding. It is a different program from TRAILBLAZER-ALZ 3. Similar names should not allow one trial's projected calendar or reported outcome to migrate into another's account.[10,18]

Even a future positive prevention trial would need to be read at its actual level of specificity. Did it enroll people without symptoms or include people with mild impairment? Was the endpoint a change in a biomarker, a cognitive score, or progression to clinical illness? How large was the effect, over what observation period, and what harms occurred in people who might otherwise have remained well for years? A favorable headline may answer one of those questions and leave the rest open. A negative trial likewise answers the question its design put to the drug, not every possible question about Alzheimer's biology.

This is why the status of an asymptomatic participant differs morally as well as statistically from the status of a patient already losing function. The prospect of slowing established decline may justify accepting burdens that would be much harder to justify for a person who feels well and may never develop symptoms. Prevention research must account for exposure among people who receive no eventual clinical benefit. ARIA does not become harmless because an intervention begins earlier; whether a prevention benefit can outweigh it is a question for controlled results.[2,3,5]

There is no contradiction between welcoming the symptomatic antibody results and declining to recommend antibody treatment as dementia prevention. The first response takes randomized outcomes seriously. The second does the same by respecting the population in which those outcomes were measured. For now, anti-amyloid antibodies hold an A

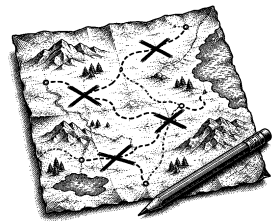
grade for slowing decline in studied early symptomatic Alzheimer's disease and Insufficient evidence for prevention. The pending programs may change the second judgment, but anticipation cannot do their work for them.[2,3,4]

Status as of October 2026

As of October 2026, the lecanemab and donanemab labels governed their approved uses, including Leqembi IQLIK's labeled use; Medicare coverage for FDA-approved anti-amyloid antibodies remained subject to enrollment in a CMS-approved registry or trial. Trontinemab had entered phase 3 testing, but the reported amyloid-clearance findings were not controlled evidence of clinical benefit.[6,7,9,14]

Verify the registry names, populations, and readout calendars for AHEAD 3-45, TRAILBLAZER-ALZ 3, PrevenTRON, and similarly named programs. Any later outcome update belongs in this dated box; it does not turn A4's negative result or a still-pending trial into a positive finding in the permanent account above.[4,13,14,18]

Chapter 20: What the Forum Got Wrong



The July account of this community ended with two different kinds of correction. In the melatonin discussions, warnings about cognitive claims and possible harms often met a settled conviction that an individual experiment was working. A few members reconsidered, but the larger discussion did not reverse course. In the taurine discussion, members were more willing to say that a familiar rationale had weakened when research challenged the idea that circulating taurine reliably falls with age. One member also reconsidered taurine after a blood-cancer concern, then revised that decision when his medical picture changed. These are dated accounts of what people said and did, not evidence that either supplement prevents dementia or caused a medical outcome. The original post pages would need to be confirmed before any of their words were quoted again.[1]

Then the archive acquired new dates. In March 2026, a controlled lithium trial in people with mild cognitive impairment missed all six of its prespecified coprimary thresholds. In April, members opened a thread about the disappointing result. In September, another lithium thread asked whether people should take the compound to prevent Alzheimer's. The sequence did not prove that nobody had changed a mind. It showed how easily a new possibility could coexist with an old negative result when the two were thought to answer slightly different questions.[2,3,4]

The NAD+ story had a similar turn, with a sharper clinical test arriving only days before this edition closed in October 2026. A February forum thread had already raised the distinction between increasing a blood marker and improving how people functioned. On October 8, the NOPARK trial reported that nicotinamide riboside had not delivered a functional

benefit in early Parkinson disease; its primary clinical comparison favored placebo. No forum response to that result appears in the posts discussed here. There is therefore no October change of mind to report, only an unanswered question about how members received the finding.[5,6]

This chapter's action is revision, not discovery. Four controlled trials gave four attractive ideas less room to make the claims their admirers wanted. Some conclusions could be narrowed without being abandoned. Others needed a plain negative verdict for the population and outcome actually tested. The forum's better moments came when members made that distinction in public; its weaker moments came when a plausible exception was treated as if it erased the main result.

The Corrections Already in the Archive

The earlier melatonin dispute is easy to flatten into a tale about credulity. That would miss the visible skepticism. Members brought contrary literature into discussions dominated by personal reports, questioned whether observations made at one exposure said anything about much larger ones, and raised possible adverse signals. Other members kept describing benefits they believed they experienced. A personal account can be sincere and still be unable to establish prevention of a disease that may develop years later.

Two propositions had become tangled. Melatonin might affect sleep or a person's immediate experience; high-dose melatonin might also protect cognition over the long term. Evidence bearing on the first proposition does not settle the second. Nor does a reported absence of problems in one person clear a substantially different exposure in another. In the July record, some members appeared to hear a challenge to the dementia claim as a challenge to what they felt each morning. That made correction harder than simply producing a citation.

The July taurine correction was less defensive. Members had discussed animal findings, aging-related measurements, and mechanistic arguments as if they belonged to one promising account. When the age-related measurement came under challenge, some were prepared to withdraw that part of the rationale without declaring every possible biological effect impossible. The member facing an uncertain blood finding made and later revised a personal decision as new clinical information arrived. Neither change established taurine's benefits or harms for a general population.

Both showed that a claim can be revised without pretending the previous uncertainty never existed.

The grade for melatonin, high-dose cognition claims, is Insufficient: no human result discussed here shows preserved cognition or prevented dementia. The grade for taurine for dementia prevention is also Insufficient. That grade does not mean an intervention has been proven ineffective at every exposure, in every population, on every possible outcome. It means the prevention claim lacks a human result that would support it. The National Institute on Aging's July 2026 explainer likewise states that nothing has yet been proven to prevent Alzheimer's disease.[1]

These grades belong to claims, not to the people who made them. A person may have slept better while using melatonin, or may have felt more energetic while using taurine. Those reports warrant respectful description as experiences. They do not turn into dementia outcomes by being vivid, numerous, or sincerely repeated. The difficulty is that prevention lacks an immediate sensation against which to check a belief. Someone can feel unchanged for years and interpret that as success, although the feared event might never have happened anyway.

The distinction also protects against an opposite mistake. A report of feeling unwell does not estimate how often a product causes harm, and a laboratory result from malignant cells cannot be applied directly to everyone consuming an ordinary food component. A correction should withdraw precisely what the new evidence undercuts. It need not make a broader claim just to sound decisive. The melatonin and taurine discussions were most informative when members could keep both thoughts in view: their own experiences were real as experiences, and the dementia-prevention verdict remained unsupported.

For the account of why an interested group can amplify both useful scrutiny and unwarranted confidence, see Book One, *The Longevity Operating System*, Chapter 13, "Supplements, Senolytics, and the Forum Effect."

That forum effect was visible again when controlled results appeared. A negative trial did not arrive on an empty desk. It arrived amid prior purchases, mechanistic explanations, stories of individual improvement, and reasonable questions about whether researchers had studied the right population. Those questions can be scientifically productive. They can also become a way to leave the original headline untouched after the test designed to examine it has failed.

Four Trials, Four Temptations

The antiviral temptation began with a causal possibility: if infection contributes to Alzheimer's disease, perhaps suppressing a virus could alter the illness. VALAD tested treatment rather than that whole account of disease origins. The double-blind trial randomized 120 HSV-seropositive people with early symptomatic Alzheimer's disease; 93 completed it, with outcomes assessed over 78 weeks. On its primary cognitive measure, the valacyclovir group worsened more than the placebo group. The between-group ADAS-Cog11 difference was 3.93 points in the direction of greater impairment, with a 95 percent confidence interval of 1.03 to 6.83. The result did not support valacyclovir treatment for this population.[7]

It also did not show that HSV could have no role in disease development. That unanswered question is the tempting exit. If someone had previously been enthusiastic about antiviral treatment, the correct update would be that this particular treatment claim encountered both a result favoring placebo and a harm signal in the tested population. Moving immediately to a different, untested prevention claim without acknowledging that result would conceal the update rather than make it. No post discussed here establishes which forum members, if any, changed their antiviral views after VALAD; it would be wrong to assign that decision to a handle merely because the decision would complete the story.[7]

Lithium offered a different escape: a hopeful subgroup inside an unsuccessful pilot. A 2025 NIH account of the underlying research described lower prefrontal-cortex lithium in samples from people with mild cognitive impairment or Alzheimer's disease, alongside experiments in mice. The mouse treatment findings were not findings in human patients. They nevertheless gave the post-discovery conversation an unusually memorable image, a substance apparently depleted in affected brain tissue and a possible way to restore it.[8]

LATTICE was a small but relevant interruption. In the single-site, double-blind pilot, 83 adults aged 60 or older with mild cognitive impairment were randomized, and 80 started treatment. After two years, none of six prespecified coprimary outcomes met the trial's significance threshold. A verbal-memory result nominally favored lithium but did not meet the stricter threshold set in advance for multiple comparisons. The authors presented the trial as evidence of feasibility, not established efficacy.[2]

In an April forum post introducing the paper, RobTuck included the central qualification: “none of the 6 coprimary outcomes reached the prespecified significance threshold.” Another participant, John_Hemming, replied, “Sorry but that was a waste of time.” Those are different reactions to the same disappointment, and neither lets this book infer what either person believed about every future lithium trial.[3,9]

The September thread shows why the story did not end in April. Its title again asked whether people should be taking lithium to prevent Alzheimer’s, while a member discussing prospective research said she was not taking lithium orotate because human results were not yet available for that form and claim. LATTICE had tested lithium carbonate in people who already had mild cognitive impairment; it did not directly test whether lithium orotate prevents dementia in people without symptoms. That distinction is legitimate. It does not turn the missed prespecified outcomes into a positive finding, or prove that the two compounds differ in a way that rescues the prevention claim.[2,10]

NAD+ presented the biomarker temptation. A forum thread in February discussed a familiar mismatch: evidence that NAD+-related measurements rise after precursor use did not consistently show corresponding functional benefits. Its posts show how members weighed that distinction, not whether the underlying studies proved a benefit. NOPARK offered a later controlled test in a different disease. Over 52 weeks, 410 people with early Parkinson disease were randomized to nicotinamide riboside or placebo, and 393 were included in the primary analysis. The clinical score worsened more in the nicotinamide-riboside group; the adjusted between-group difference was 2.72 points, favoring placebo. The investigators concluded that their findings did not support nicotinamide riboside as a disease-modifying Parkinson treatment.[5,6]

Parkinson disease is not Alzheimer’s disease. NOPARK cannot answer whether an NAD+ precursor prevents dementia. It can test a more general argument often used to carry enthusiasm across conditions: that moving a blood biomarker in the desired direction makes clinical benefit likely enough to presume. The trial’s clinical result gives no license for that inference. A raised marker shows that an intervention engaged something measurable; it does not show that the measure lies on a causal path to preserved function.[6]

The fourth temptation was to let a prevention hypothesis erase a treatment failure. The evoke and evoke+ trials enrolled 3,808 people with

amyloid-confirmed early symptomatic Alzheimer's disease and followed participants for up to 156 weeks. Their primary clinical comparison, change on the Clinical Dementia Rating–Sum of Boxes at week 104, did not significantly favor oral semaglutide in either trial. The investigators concluded that it did not slow progression in that population.[11]

The biological measurements make the verdict more, not less, instructive. An analysis published after the trial presentations described small changes in cerebrospinal-fluid biomarkers, a fall in an inflammatory blood marker, and weight loss, without a corresponding clinical benefit. These were not signs that the primary outcome had secretly succeeded. They showed that a drug can produce measurable peripheral effects while the outcome patients and families most need remains unchanged.[11,12]

As of October 2026, no GLP-1 drug is approved to prevent or treat Alzheimer's disease or dementia. Whether a GLP-1 drug could prevent disease when used earlier remains an unresolved hypothesis, not a demonstrated benefit and not the result tested by evoke. Equally, the trials' failure to treat early symptomatic disease does not logically disprove every possible prevention study. The honest sentence has both halves: treatment missed its clinical endpoint in the tested population; prevention still needs a trial capable of answering that different question.[11,12]

For how GLP-1 drugs work and what the evidence says about semaglutide in its approved uses, see Book Four, *The Metabolic Frontier*, Chapters 3 and 6.

A timeline makes these verdicts easier to see than a tally of who sounded optimistic. The point is not to rank forum members by how quickly they conceded. It is to show when a claim became attractive, what the controlled test asked, and which uncertainty remained afterward.

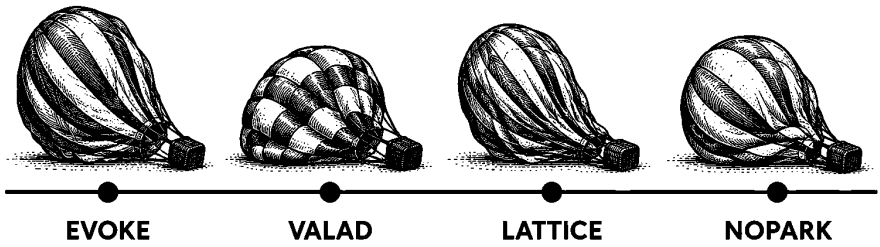


Figure 13. A year of clean failures, 2025–2026: evoke (oral semaglutide in early Alzheimer's), VALAD (valacyclovir; cognition slightly worse than placebo), LATTICE (low-dose lithium; prespecified endpoints missed) and NOPARK (nicotinamide riboside in Parkinson's disease).

Figure 13. A timeline of enthusiasm and trial verdicts: the 2025 antiviral treatment result in VALAD; the 2025 lithium discovery report followed by LATTICE's March 2026 missed prespecified outcomes; the February 2026 NAD+ biomarker debate followed by NOPARK's October functional result; and the evoke program's clinical miss, reported in 2026 after its earlier presentation. Each verdict applies to its tested population and outcome, not to every related prevention hypothesis.[2,5,6,7,8,11,12]

The four trials differed greatly in population, size, and claim. They belong together here because each put pressure on a favored bridge from plausibility to benefit. VALAD tested whether an antiviral rationale yielded cognitive improvement in early symptomatic Alzheimer's and found a result in the wrong direction. LATTICE tested whether a lithium signal survived prespecified comparisons in mild cognitive impairment and did not establish efficacy. NOPARK showed how a promising biological intervention could miss a functional endpoint in Parkinson disease. Evoke asked whether a metabolic drug slowed clinical progression in early symptomatic Alzheimer's and found that it did not. No single verdict settles the prevention of all dementia. Each changes what may responsibly be said about the question it actually examined.[2,6,7,11]

Updating Versus Explaining Away

An update begins by keeping the tested claim still long enough to hear the answer. “This intervention did not improve this prespecified clinical endpoint in this population” is often an uncomfortable sentence. It may coexist with reasons to run another trial. It cannot be replaced by those reasons. In LATTICE, for example, the nominal verbal-memory difference can inform a future hypothesis, but the authors’ feasibility conclusion and six missed coprimary thresholds remain the reported outcome of this pilot.[2]

Explaining away starts with the exception and leaves the original enthusiasm unmarked. Perhaps the exposure was wrong, the population too ill, the follow-up too short, or the compound’s formulation unlike the one a member favored. Each could be a question worth testing. None is a result. The boundary is whether a speaker can say what finding would actually cause the preferred claim to lose support. If every miss points to a newly specified version of the same promise, the promise has ceased to be readily testable.

The antiviral case exposes a subtler distinction. Treatment after symptoms appear and prevention before symptoms appear are different questions. VALAD cannot settle the latter. But someone who advocated valacyclovir *as treatment* cannot report the trial merely as neutral toward an infection theory. The observed cognitive difference favored placebo and raised a safety concern in early symptomatic Alzheimer’s. A possible role for HSV in disease development deserves its own evidence, not protection borrowed from the question VALAD left unanswered.[7]

EvOKe calls for a similar discipline, with an added complication: semaglutide has established uses outside Alzheimer’s disease. A drug’s benefits in another condition can make a dementia hypothesis more plausible and attract serious research. They cannot be counted again as proof that it slows Alzheimer’s progression after two large trials fail on the designated clinical measure. The modest biomarker movements reported alongside evoke may help researchers frame questions; they do not overturn the clinical comparison.[11,12]

The NAD+ argument is particularly vulnerable to this reversal because biomarkers feel precise. Blood can yield a number, the number can move, and the movement can be reproduced. A cognitive or functional outcome is noisier, slower, and more affected by daily life. Precision does not make the biomarker more important than the clinical question. If the proposed

purpose is preserved function, a functional miss cannot be dismissed simply because a laboratory measure responded. NOPARK is a Parkinson trial, so its verdict must remain a Parkinson verdict, while its warning about surrogate reasoning travels more widely.[6]

There is also a fair limit to negative evidence. A pilot such as LATTICE is not a definitive test of every lithium hypothesis; its authors did not call it one. NOPARK did not enroll people seeking Alzheimer's prevention. VALAD studied seropositive patients with early symptomatic disease, not infection prevention across a lifetime. Evoke tested treatment after Alzheimer's symptoms had begun, not prevention before them. Respecting those limits is not evasive. It becomes evasive only when the limitation is used to restore the exact claim that the trial tested and failed to support.[2,6,7,11]

The dated forum posts support a modest account of what happened socially. April's lithium thread acknowledged the missed thresholds, and September's thread returned to a prevention question. The February NAD+ thread considered the biomarker–function gap before NOPARK was published. Those posts do not show how the members responded to the October trial, nor do they establish a comparable exchange after the VALAD or evoke results. Other reactions, quietly dropping an idea, changing only its wording, or defending it more fiercely, are possible, but none can be attributed to a handle without a post.[3,5,6,7,10,11]

For the practice of recording a verdict and then changing it when the evidence changes, see Book One, *The Longevity Operating System*, "Source Appraisal Handbook."

A written verdict has an advantage over memory. Memory tends to preserve the reason an intervention first seemed interesting and blur the exact claim made on its behalf. A dated statement can say that a hypothesis was plausible before a trial, that the trial missed a specified outcome, and that a narrower question remains open. It need not turn uncertainty into certainty in either direction.

A Community's Better Habit

The forum's useful habit was not skepticism as a personality trait. Skeptics can be selective too. Its useful habit was occasionally to put a paper beside an earlier expectation and ask what, specifically, had changed. The July taurine discussion showed that in a relatively forgiving setting: members could question an age-related rationale without resolving every possible effect of taurine. The lithium posts showed both the value and the difficulty of doing it after a controlled result: the missed thresholds could be stated plainly even while a distinct prevention question continued to interest readers.[2,3,10]

This is a better standard than demanding that members stop caring about an idea the moment a trial fails. Curiosity has a place after a miss. Researchers might study a different disease stage, improve a design, or test a proposed mechanism directly. But curiosity should carry the negative result forward. Otherwise the next discussion begins as though nothing had been learned, and each new rationale becomes a fresh account of why the old headline might still be true.

The asymmetry matters most in dementia prevention. A person living without dementia today cannot observe the disease that did not occur, much less identify which habit or product prevented it. Forum members often have unusually detailed records of sleep, laboratory measures, and perceived mental performance. Those records can help them describe their experience; they cannot manufacture an untreated comparison group or compress decades of risk into a few months of feeling well. The archive is richest where it records that limit rather than claiming an answer from the absence of symptoms.

It is worth preserving the warmth of the record alongside its mistakes. A member who raised a potential adverse signal was not merely "anti-supplement"; a member who kept an open question alive after a null trial was not necessarily refusing evidence. People were trying to make decisions while papers arrived out of order and addressed different populations. That human difficulty does not excuse overclaiming. It explains why an explicit, dated correction is more useful than either ridicule or a flattering story in which everyone promptly sees the light.

As of the October 2026 cutoff, the four controlled verdicts were available, but the community's response to each was not equally visible. VALAD gave no support for treating early symptomatic Alzheimer's with valacyclovir and raised a harm signal. LATTICE did not establish lithium efficacy in

mild cognitive impairment. NOPARK did not support nicotinamide riboside as a disease-modifying Parkinson treatment. Evoke did not show that oral semaglutide slowed early symptomatic Alzheimer's. The unanswered prevention questions remain unanswered, not secretly positive, and not all disproved by trials of treatment or another disease.[2,6,7,11]

The melatonin and taurine discussions showed resistance and reconsideration, but neither established efficacy. The later trials gave controlled answers, though only to the questions they tested. A community earns trust not by having guessed every verdict in advance. It earns some trust when members can see an attractive claim become narrower, a negative result remain negative, and an open question remain open.

Chapter 21: What This Doesn't Prove



A person reports a striking change: the forgotten security code comes back, or a workout that had felt punishing suddenly feels easy. The account is arresting because it is specific. It belongs to a life, not a spreadsheet. In the forum, such accounts often arrived before the larger studies had answered the question that mattered most to the person posting.

Now set that moment beside a controlled trial. The evoke and evoke+ trials asked whether oral semaglutide slowed clinical decline in 3,808 people with amyloid-confirmed early symptomatic Alzheimer's disease. At the primary assessment, 104 weeks, it did not significantly improve the clinical outcome in either trial.[1] The individual account and the trial need not be about the same intervention to reveal the difficulty. One asks, *What happened to me?* The other asks, *Compared with what would have happened otherwise, did this intervention change a defined outcome in a defined population?* Both questions deserve to be heard. They cannot answer for each other.

This chapter is a pause after the claims examined in the preceding chapters. It is not a correction to the warmth or intelligence of the people who made them. It is a boundary around what their reports, and the studies beside them, can establish. The National Institute on Aging's position remains plain: nothing has yet been proven to prevent Alzheimer's disease. It treats blood-pressure management, physical activity, and other general health measures as reasonable steps while prevention research continues.[2] That distinction, reasonable care versus proven prevention, will govern the final chapter's two lists.

A Claim Changes Lanes

“The study found” is a remarkably elastic phrase. It may refer to a registered plan, a conference abstract, a preprint, a peer-reviewed report, a replicated result, or a conclusion incorporated into a guideline. These are not interchangeable publications. A protocol establishes what investigators intended to measure. An abstract may announce a result without enough detail to inspect it fully. A preprint exposes more methods and results but has not undergone journal review. Peer review adds scrutiny, not a certificate of truth; replication tests whether a result survives another setting. A guideline must weigh findings against harms, alternatives, and the realities of care. This is the publication ladder, not a ranking in which every paper on a higher rung is necessarily better than every paper below it.

The ladder matters because a claim can gain authority without gaining evidence. A forum member finds an abstract; a discussion calls it a study; a later account calls it a published trial. No one need intend to mislead. Each retelling merely drops a qualification until the surviving sentence sounds more settled than the underlying work. In the rapamycin research discussed earlier in this book, the July review found a conference abstract, a peer-reviewed follow-up, registry results, a results preprint, and a registered study without posted results being discussed in the same broad conversation. They represented different amounts of available detail and scrutiny. As of October 2026, ERAP’s main report remained a preprint, and REACH had no posted results; those statuses should be verified again before either is described as a definitive clinical finding.

Publication is only one lane change. A study may be excellent at answering a narrower question than the headline attached to it. A controlled trial showing a small improvement on a cognitive composite has not, by that fact alone, shown that fewer people develop dementia. A trial in people who already have Alzheimer’s cannot establish prevention in people without symptoms. Conversely, a trial that finds no benefit on its chosen endpoint does not prove that every conceivable use of an intervention is futile. The defensible sentence keeps the population, comparator, duration, and outcome attached to the result.

Design buys some of that defensibility. Random assignment helps make groups comparable at the outset; a concurrent control shows what occurred over the same stretch of time without the tested intervention. Blinding limits changes in reporting and assessment that knowledge of an assignment can produce. A prespecified primary outcome restrains the

temptation to search many measurements and lead with whichever moved. An open-label before-and-after study can establish that a project was feasible and identify questions worth testing. It cannot by itself rule out test familiarity, regression toward an average, changes in other care, or selective follow-up.

For the fundamentals of why designs support different claims, see Book One, *The Longevity Operating System*, Chapter 2, "The Hierarchy of Evidence."

Observational work has its own strengths. Consider the Welsh shingles-vaccine study. Eligibility changed sharply at a date-of-birth cutoff, creating groups close in age but very different in vaccine uptake: 47.2 percent among those just eligible, versus 0.01 percent among those just ineligible. The primary analysis included 282,541 people without dementia at baseline. Over seven years, the investigators estimated that vaccine receipt was associated with a 3.5-percentage-point lower probability of a new dementia diagnosis, a 20.0 percent relative reduction. It was a thoughtfully designed natural experiment, not a randomized trial.[3]

The difference is not a ceremonial objection. Eligibility is not receipt, and people born near a cutoff can still differ in ways that matter to an outcome measured years later. A 2026 commentary questioned whether very large implied effects in related Canadian analyses could plausibly represent protection against all-cause dementia without some inflation from bias. It also noted that, in Wales, the declines in shingles and dementia occurred concurrently rather than a decline in shingles clearly preceding the dementia decline.[4] Those objections do not erase the Welsh finding. Nor does the Welsh finding settle the causal question. A natural experiment can sharply improve on a loose comparison of vaccine recipients and nonrecipients while leaving possibilities that random assignment would address differently.

A randomized outcome, in turn, is only as broad as the trial that produced it. A null result in one population, over one follow-up period, cannot be stretched into a universal law. Nor should the absence of a dementia-prevention trial make a well-observed natural experiment worthless. The useful contrast is between what each design excludes and what each still allows. For shingles vaccination, that means taking the observational signal seriously without selling the vaccine as proven dementia prevention. The research question remains open even as vaccination has reasons to be considered on its own merits.

When the Marker Moves Alone

A marker can change long before a clinical outcome is visible. That makes markers attractive in a disease whose course can extend over years. It also makes them easy to overinterpret. A measure of exposure or biological response tells us that something happened in the body. The claim readers care about is usually farther downstream: whether thinking, daily function, or the chance of developing dementia changed. The intervening links have to be demonstrated, not assumed.

NAD+ offers a particularly clear example. Raising a blood level of NAD+ may show that a precursor engaged its intended biochemical target. It does not establish that neurons function better, that memory is preserved, or that dementia risk falls. The distinction is visible in a disease other than Alzheimer's: in the 52-week NOPARK trial, 410 people with early Parkinson disease were randomized to nicotinamide riboside or placebo, and 393 were included in the primary analysis. The clinical score worsened more in the nicotinamide-riboside group; the authors concluded that the findings did not support it as a disease-modifying Parkinson treatment.[5] This was not a dementia-prevention trial, and Parkinson's disease is not a substitute population for one. It is a warning against allowing target engagement, including a rise in NAD+, to stand in for uncertain function.

A marker may fail as a stand-in for several reasons. It might be measured in blood while the hoped-for benefit concerns the brain. It might lie on a pathway the intervention changes without changing the disease process that matters. Or a biological change might be real yet too small, too brief, or too late to alter a person's abilities. Those are distinct failures; a trial that measures both marker and function can begin to separate them. A marker result alone cannot.

The evoke trials give this problem clinical weight. Biomarker findings generated interest, but the trials' primary question concerned change on the Clinical Dementia Rating–Sum of Boxes, a measure of clinical status. Across two randomized trials involving 3,808 people with early symptomatic Alzheimer's, semaglutide did not significantly slow decline on that primary outcome at 104 weeks. The investigators concluded that it did not slow clinical progression in the population studied.[1] A secondary biomarker movement cannot reverse that primary clinical verdict. It may suggest a biological effect worth understanding; it does not convert a negative clinical trial into a positive one.

The reverse caution also applies. A disappointing clinical result does not prove that every measured biological change was an artifact. It means the changes, as observed under the tested conditions, did not deliver the prespecified clinical benefit. Keeping both sentences intact protects against two common reactions: discarding all the laboratory findings because the trial failed, or promoting a favorable laboratory finding because the trial failed. The first throws away a possible research clue. The second asks that clue to do a completed trial's job.

Some measurements are especially vulnerable to a shift in purpose. A blood test developed to help evaluate a person with symptoms is not thereby a suitable screening test for someone who feels well. The U.S. Preventive Services Task Force found insufficient evidence to assess the balance of benefits and harms of screening community-dwelling adults aged 65 and older who have no recognized signs or symptoms of cognitive impairment; its statement does not address evaluation when symptoms are present.[6] A result can be analytically impressive and still raise unanswered questions about what should happen next, including false alarms, distress, and downstream testing. As of October 2026, no Alzheimer's blood test is cleared to screen people without symptoms.

The more personal a marker feels, the harder this restraint can be. A scan is an image of someone's own brain; a blood result arrives with a number and a reference range. Neither is imaginary. Yet an individual result does not reveal what the same person's life would have looked like without an intervention. Clinical outcomes, controls, and adequate follow-up remain necessary precisely because the measurement is real.

The Limit of One Person

The forum's accounts deserve to be read with the generosity due any first-person report. People can accurately describe what they noticed without being able to identify its cause. The gap is not a defect of honesty. If memory seems sharper after a change, expectation, sleep, practice on a familiar task, an unusually poor week beforehand, and the intervention itself may all remain possible explanations. A reader can believe the person and still decline the causal claim.

An N-of-1 comparison can sometimes sharpen an individual question. Short-term effects that can be measured repeatedly are more tractable than outcomes that may take years to appear. Alzheimer's prevention is unusually resistant: risk changes with age, cognitive tests can improve

through practice, other habits and treatments change, and an intervention's effects may not stop neatly when observation stops. The desired endpoint cannot be watched appearing and disappearing within one person. For what individual comparisons can and cannot establish, see Book One, *The Longevity Operating System*, Chapter 11, "N-of-1."

Even an exceptionally careful personal account would have a second limit. It concerns one person selected by circumstance, motivation, health, and willingness to report. Population prevention asks what happens, on average and with what harms, among people who do and do not receive an intervention. It asks whether any apparent benefit extends beyond an unusual responder, and whether people who fared poorly were equally likely to be heard. A forum archive can preserve a vivid success while never collecting the denominator: everyone who tried something, noticed nothing, and left.

Nor is a short improvement in attention equivalent to avoiding dementia. Those are different outcomes on different timescales. The National Institute on Aging's statement that prevention has not yet been proven is not a dismissal of individual experience; it is a refusal to promote that experience past the question it can answer.[2] Forum members have identified scientific findings early and questioned weaknesses in their own favored theories. Speed and discernment make the forum useful as a source of questions. They do not supply a comparison group or long-term outcomes.

There is a quieter use for first-person observation. A symptom or unexpected measurement arising during a self-experiment may call attention to a possible harm even when it cannot establish efficacy. Such a report is a signal to take seriously, not an estimate of how often the harm occurs or proof of what caused it. The asymmetry matters: a person need not prove population risk before treating an alarming experience as a reason to stop and seek accountable care.

The Ethical Stop Line

Consent begins with an honest account of uncertainty. Someone discussing an intervention for dementia prevention should be able to distinguish established uses from the hoped-for use, clinical outcomes from markers, and a monitored research study from an informal experiment. Approval for one condition does not confer approval for prevention in people without symptoms. Off-label use of an approved drug is a clinical question, not a conclusion licensed by this book's evidence.

The forum also holds information people disclosed in a particular social setting: family history, worries about memory, test results, and accounts of self-experimentation. Public access does not remove the obligation to preserve context. The July account used public handles, did not diagnose participants, and did not treat a person's silence as evidence of improvement, decline, safety, or death. It did not claim private confirmation where there had been none. A careful retelling should not turn another person's uncertainty into a more confident story merely because confidence reads better.

Stopping is the other half of consent. Uncertainty is not meaningful if every unwelcome result can be explained away afterward as temporary, promising, or unrelated. An accountable decision has room for harms, competing explanations, and the possibility that the hoped-for benefit is absent. It also has a boundary beyond which an experiment should not simply continue by force of enthusiasm. This chapter does not set personal thresholds or offer an experimental protocol. For safety, consent, and stopping rules, see Book One, *The Longevity Operating System*, Chapter 17, "Safety, Consent, and Stopping Rules."

There is an ethical limit to what this account can ask readers to infer from published research, too. The USPSTF's insufficient-evidence statement on screening adults without recognized symptoms is not a recommendation to ignore symptoms; it marks the difference between offering a test broadly and evaluating a concern that already exists.[6] Similarly, a treatment trial in early symptomatic Alzheimer's and an observational signal among people initially free of dementia occupy different places in a prevention argument. Treating either as an answer to every adjacent question risks exposing people to decisions that the evidence has not earned.

A remembered code. A changed blood marker. A sharp vaccination cutoff. A large trial with a null clinical result. Each is an observation, and each has a limit that belongs in the same sentence as the finding. The forum is at its

best when it keeps reading past the headline, including when the headline is one it wanted to believe.

What follows in the final chapter is not a verdict on the people who tested ideas before answers were available. It separates actions supported for health on their own merits from hypotheses still worth watching. That distinction leaves room for curiosity without making uncertainty sound like permission.

Chapter 22: Two Lists: What to Do Now, What to Watch



A watch list is an attractive way to end a book about Alzheimer's. It promises that the next trial, the next blood marker, the next correction to an old assumption will not pass unnoticed. The July version of this ending leaned into that impulse. It treated uncertainty as something to record rather than fill with a protocol: name the population, specify the outcome, keep the negative findings, and decide in advance what would change your mind.

That remains useful. But a watch list alone would give the most experimental questions the last word. It would leave ordinary clinical concerns, blood pressure, diabetes, smoking, hearing, looking less interesting precisely because they are familiar. The better ending has two lists, graded for different purposes. One belongs in a clinical conversation now. The other belongs on a dated research watch. Neither is a prescription, and the second is emphatically not a shopping list.

The distinction returns us to the question Deborah Hall asked on Easter Sunday in 2024. She had already ordered a bottle and wanted to know whether the idea behind it deserved her confidence; the record does not say what she eventually decided. The answer available now is not a verdict on that private decision. It is a clearer account of which claims have crossed from possibility into controlled human evidence, which have not, and what a blood test can, and cannot, settle before symptoms appear.

The Short List for a Clinical Conversation

Blood pressure leads this list because the outcome evidence is unusually close to the question readers care about. In a cluster-randomized trial involving 33,995 adults aged 40 or older with uncontrolled hypertension in 326 rural Chinese villages, a village-doctor-led intervention was associated with less all-cause dementia than usual care after four years: a risk ratio of 0.85, with a 95 percent confidence interval of 0.76 to 0.95. Serious adverse events were fewer in the intervention group.[1] That is a dementia outcome, not merely a change on a memory test.

It is not a universal blood-pressure target. The Chinese trial compared systems of care in a particular population with uncontrolled hypertension; it did not establish that every older adult should seek the trial's target, regardless of frailty, falls, other illnesses, or treatment burden.[1] SPRINT MIND supplies an instructive contrast. Among 9,361 adults with hypertension, intensive control reduced mild cognitive impairment, but its reduction in probable dementia was not statistically significant over a median 5.11 years of follow-up. The trial stopped its intervention early for cardiovascular benefit.[2] Taken together, the studies make blood-pressure care the strongest intervention-specific prevention conversation in this book, with a B headline grade: a controlled human signal with limits, not an individual guarantee or a target to copy.

This is also where the difference between *discussing an established condition* and *requesting an Alzheimer's intervention* matters. Blood-pressure decisions have cardiovascular and kidney consequences beyond cognition. A person whose readings have changed, whose medicines cause symptoms, or whose existing plan is hard to follow brings a clinical problem that exists whether or not any dementia trial succeeds. The evidence here gives that conversation added weight. It does not turn a book into the person setting the plan.

Physical activity sits close to blood pressure in practical relevance, but not at the same dementia-evidence grade. A 2026 synthesis of randomized trials in cognitively healthy adults aged 60 or older found small improvements in executive function with aerobic and resistance exercise. Its pooled estimates were 0.130 and 0.232 standard deviations, respectively.[3] That supports B for a measured cognitive benefit. The headline claim that exercise prevents dementia remains C, observational human evidence rather than a demonstrated reduction in diagnoses.

Exercise has reasons to be discussed beyond Alzheimer's; those reasons should not be used to smuggle in a stronger dementia claim.

The distinction protects exercise from two opposite distortions. Calling a small test-score gain a proven prevention effect asks too much of the trial. Calling exercise irrelevant because incidence has not been established asks too much of that absence. Cognitive tests measure something worth studying, but they are not interchangeable with years lived without dementia. For the broader treatment of fitness as a longevity intervention, see Book One, *The Longevity Operating System*, Chapter 5.

Structured multidomain programs earn B for cognition, again not for dementia incidence. FINGER compared a two-year combination of diet, exercise, cognitive training, and vascular-risk monitoring with general health advice in 1,260 at-risk older adults; the intervention had a small advantage on a cognitive-test composite.[4] US POINTER randomized 2,111 at-risk adults aged 60–79 for two years; both its structured and self-guided groups improved, while the structured group improved more, by 0.029 standard deviations per year. Dementia incidence was not tested.[5] LatAm-FINGERS, conducted across 11 Latin American countries, likewise found a greater two-year improvement in global cognition with a systematic program than with a more flexible comparison.[6]

These studies make organization and sustained support plausible contributors to measured cognitive performance. They do not isolate a magic component. Nor do their results tell us that every person can obtain or maintain the same kind of program. The more demanding LatAm-FINGERS intervention also reported more adverse events, although none of its serious adverse events was judged intervention-related.[6] Access, cost in time, disability, and adherence belong in the interpretation of a real-world program, even when a trial's principal comparison favors the structured arm. For the broader dementia-prevention synthesis, see Book One, *The Longevity Operating System*, Chapter 15.

Hearing belongs on the short list because hearing loss is worth addressing in its own right, not because hearing aids have passed a definitive dementia-prevention test. The chapter's headline grade remains C, with a B-null result for the primary overall randomized comparison and a more favorable signal in a high-risk subgroup. A 2026 observational analysis estimated lower seven-year dementia risk under a hearing-aid prescription strategy, but overall cognition was similar between strategies, and its authors warned that residual confounding could remain.[7] Those are

different findings, not votes to average. A subgroup may help identify whom a future trial should study; it does not erase a null primary result.

Diabetes care also stays on the clinical list without being sold as Alzheimer's prevention. Its dementia headline is C: observational human evidence whose causal interpretation remains unsettled. A 2026 English cohort examined routinely measured cardiometabolic factors among 249,958 adults with type 2 diabetes and recorded 22,492 dementia cases. Associations involving glucose measures varied by follow-up period, with evidence of nonlinearity and possible reverse causation when follow-up was shorter than five years.[8] A change in measured glucose can be important for diabetes care without supplying a reliable conversion into future dementia cases avoided. For the related metabolic-drug questions, see Book One, *The Longevity Operating System*, Chapter 14.

Smoking belongs in the established risk-factor discussion, though this closing synthesis assigns it no newly invented intervention grade. Avoiding tobacco exposure has health grounds independent of a promised Alzheimer's effect. The same discipline applies to recommended older-adult vaccines: their indications stand on prevention of the infections for which they are recommended, not on a claim that vaccination has been proved to prevent dementia. The National Institute on Aging's 2026 account says that nothing has yet been proved to prevent Alzheimer's disease, while treating general health measures as reasonable.[9] CDC's shingles-vaccine recommendation is for shingles prevention; dementia is not part of that indication.[10]

The dementia findings on vaccination are nevertheless worth taking seriously at their proper grade. A Welsh natural experiment compared people just eligible with those just ineligible for an earlier shingles vaccine. Among 282,541 people without dementia at baseline, estimated vaccine receipt was associated with a lower probability of a new dementia diagnosis over seven years. Eligibility created a sharp difference in uptake, making the design more informative than an ordinary comparison between people who chose vaccination and people who did not. It was still not a randomized vaccine trial with dementia as its outcome.[11] C means an observational human signal, not a licensed dementia-prevention use. The finding deserves replication and scrutiny, including whether effects differ across vaccines and populations; it does not alter what the vaccine is recommended for.

This first list is deliberately uneven. Blood pressure has a randomized dementia result; multidomain programs and exercise have stronger claims for cognitive testing than for diagnoses; hearing has a null overall randomized finding alongside a high-risk signal; diabetes and vaccine associations remain observational. The list is united not by one grade but by a practical distinction: these subjects already have legitimate clinical or public-health reasons to be discussed. Their possible brain benefits should be stated at the strength the evidence allows.

A clinician conversation need not arrive as a proposed protocol assembled from chapters. It can begin with the condition, symptom, or uncertainty actually present, then ask what evidence applies to that person's situation. For turning concerns into questions without turning them into instructions, see Book One, *The Longevity Operating System*, Clinician Conversation Handbook.

The Watch List Is Not a Protocol

The second list has a lower threshold for *interest* and a higher threshold for *action*. Its entries merit attention because an answer may be forthcoming, not because a person should try to reproduce a trial. In the July ending, the watch-list rule was to follow a specific claim, population, comparator, outcome, publication state, rather than a molecule's reputation. It also required an adverse-signal record, so that attractive biomarkers would not be remembered more faithfully than null results or harms. That rule matters still more when a study concerns an intervention with meaningful risks.

Prevention antibodies are the clearest example. Antibodies used to treat early symptomatic Alzheimer's disease have a different evidence claim from giving an antibody to someone without cognitive symptoms. As of October 2026, those approved treatments remain treatments for eligible people with early symptomatic disease, not approvals for prevention in people without symptoms. TRAILRUNNER-ALZ 3 is a randomized phase 3 study designed to assess remternetug in preclinical Alzheimer's disease and mild cognitive impairment, with time to clinical progression as its primary endpoint. Its published conference abstract describes the study and enrollment, not an efficacy result.[12] The prevention headline is therefore Insufficient: the outcome that could establish benefit has not been reported.

This watch item requires particular care with the word *preclinical*. A positive biomarker in a person without symptoms does not itself mean that treatment will improve a life the person can feel or measure. A convincing upgrade would have to show less clinical progression in the intended population, in a credible randomized comparison, with harms weighed against that benefit. The possibility of adverse effects is not an afterthought reserved for the day after a positive press release.

Glymphatic claims occupy an earlier part of the watch. Brain-fluid-clearance mechanisms are scientifically interesting, and imaging may make them more testable. But Insufficient is the prevention grade for proposed glymphatic "enhancement": imaging or preclinical plausibility has not established that an intervention delays cognitive decline or dementia. A better image of clearance would be an observation to explain, not the clinical result itself. This is one place where the watch list can be useful without pretending that a mechanism has become a therapy.

Devices deserve separate entries rather than a single "brain stimulation" verdict. The 40 Hz light-and-sound HOPE study is a randomized, sham-controlled trial in people with mild to moderate Alzheimer's disease, not a prevention trial in cognitively healthy adults. As of October 2026, its registry listed the study as completed, but no topline efficacy result had been posted or announced. Its primary endpoint combines cognitive and daily-function measures.[13] That makes the completed trial important to watch. It does not make a consumer device a substitute for the trial's comparison, and even a favorable treatment result would not automatically establish prevention. Other device claims need their own population, control condition, clinical outcome, and safety assessment.

GlyNAC is another named item whose familiarity can outrun its evidence. As of October 2026, a registered randomized study comparing GlyNAC with placebo in people who have Alzheimer's disease was active, not recruiting, and had no posted results. It planned to assess cognition alongside metabolic and biological measures.[14] The prevention headline remains Insufficient. A change in glutathione-related biology, if found, would help investigate mechanism; it would not alone show that people without dementia remain well longer. For the fuller discussion of GlyNAC as a supplement claim, see Book One, *The Longevity Operating System*, Chapter 13.

GLP-1 prevention is worth watching precisely because an attractive story has already met a hard result in a neighboring population. Two phase 3 trials involving 3,808 people with early symptomatic Alzheimer's disease found that oral semaglutide did not slow decline on their principal clinical measure over 104 weeks; the trials were discontinued. That is B-null for the treatment endpoint tested, not proof that every prevention hypothesis is false. It should, however, make a prevention claim less willing to lean on metabolic mechanisms or observational associations alone. No GLP-1 drug is approved to prevent or treat Alzheimer's disease or dementia as of October 2026.

PROTECT-Cog, announced in July 2026, proposes to examine a multidomain lifestyle approach with a metabolism-targeting drug such as a GLP-1 agonist. Its announcement described planned follow-up and comparisons, not outcomes.[15] A combination study also poses a demanding interpretive question: if a result is favorable, which comparison shows what the drug added beyond the lifestyle intervention? That is why GLP-1 prevention stays Insufficient rather than borrowing the B cognitive grade of structured lifestyle programs or treating a drug's established indications as evidence for a new one. For how GLP-1 drugs work, see Book Four, *The Metabolic Frontier*, Chapter 3.

The watch tier is not restricted to these four families of claims. It is a method for keeping a research question open without silently turning it into a personal experiment. Trials with incomplete or outdated registry entries illustrate why "no results posted" describes the state of knowledge, not whether an intervention worked or failed. A registry can identify a planned endpoint or report that a study is complete; it cannot provide an outcome that has not been posted. The distinction is especially useful when a headline says a trial is "underway," although the comparison needed to judge its claim remains unavailable.

Write the Upgrade and Downgrade Triggers

A watch list becomes more honest when its verdict can move in both directions. “More research is needed” says almost nothing unless it identifies what sort of research would matter. An upgrade for prevention antibodies would be a well-conducted randomized result showing less clinically meaningful progression in people without symptoms or at the precisely defined early stage under study, with adverse events fully reported. A downgrade would be no clinical advantage despite a biological effect, or a burden of harm that makes any small advantage untenable. TRAILRUNNER-ALZ 3 has specified clinical progression as its primary outcome; the available abstract does not yet tell us the answer.[12]

For glymphatic interventions, an imaging change is not an upgrade to prevention. The trigger is a controlled result on cognition, function, or disease progression in the population named by the claim, accompanied by credible safety evidence. A repeated absence of such benefit, or evidence that the intervention worsens sleep or function while improving a favored image, would lower confidence. This does not require rejecting glymphatic research. It requires declining to substitute its proposed mechanism for the outcome patients and families need.

For HOPE and other devices, publication of the prespecified clinical and functional comparison, together with adverse events and an account of missing data, would move the *symptomatic treatment* claim. HOPE’s completed status without announced efficacy results cannot do that work.[13] A null sham-controlled clinical result would downgrade the treatment claim even if a physiological signal were intriguing. Prevention would remain a separate question either way: a trial in people already living with Alzheimer’s disease cannot, by itself, answer whether a device prevents its onset.

For GlyNAC, the registered trial can test a treatment question in people with Alzheimer’s disease, not establish prevention in people without it. No results were posted as of October 2026.[14] Favorable biological markers without a credible clinical difference would leave the prevention grade where it is. A clear null cognitive result or meaningful harm would also deserve a place in the record, rather than being set aside on the grounds that another formulation or population might someday work.

For GLP-1 prevention, an upgrade needs a controlled prevention-relevant outcome, with the added contribution of a drug separable from the effects of the accompanying program. PROTECT-Cog has announced that it will

assess adding a metabolism-targeting drug, but has reported no trial outcome.[15] A null result on its clinical question, or harm that offsets benefit, would downgrade the specific combination claim. The null early-symptomatic semaglutide trials should remain visible beside any future positive surrogate result: neither finding answers every possible population, but neither may be erased to make the other easier to tell.

This habit applies to the short list as well. A new trial could strengthen an exercise-to-dementia claim without changing what its earlier cognitive trials measured. A failed dementia-incidence trial would not cancel exercise's other health effects. A replication of the high-risk hearing finding would sharpen its relevance; another null overall result would still need to be reported. The grade follows the stated claim, population, and endpoint. It is not a lifetime award attached to an intervention's name.

The grades used here preserve those assigned intervention by intervention in Chapters 2–20; this closing synthesis creates no new grade. A denotes a replicated clinical outcome in the relevant population, B a controlled human signal with limits, B-null controlled evidence of no effect on the endpoint tested, C observational or uncontrolled human evidence, D preclinical work, and E an account or hypothesis. Insufficient means the particular claim has not reached even a useful fit within those lanes. A treatment grade cannot simply be carried across to prevention, and a cognitive-test grade cannot be relabeled a dementia-incidence grade.

A dated record helps keep that discipline when the field changes. It should retain the old conclusion, add the new study, and say why the grade moved, or why it did not. For maintaining a trial watch without losing track of study populations and endpoints, see Book One, *The Longevity Operating System*, Source Appraisal Handbook.

An Answer Without a Guarantee

The two lists give different kinds of permission. The clinical-conversation list permits serious attention to conditions and concerns that already matter, while keeping Alzheimer's-specific claims proportionate to their evidence. The watch list permits curiosity, even excitement, without asking a reader to become an uncontrolled trial. Neither turns uncertainty into passivity. Waiting for a clinical outcome can be an active decision about what counts as an answer.

Blood tests bring the distinction back to Deborah Hall's original question. As of October 2026, FDA-cleared Alzheimer's blood tests aid assessment of people with signs, symptoms, or complaints of cognitive decline; they are not cleared as screening tests for people without symptoms.[16,17] The FDA says its cleared Lumipulse test is neither for screening nor a stand-alone diagnosis. Roche likewise says its cleared pTau217 test has not been established to predict who will develop dementia.[16,17] Separately, the U.S. Preventive Services Task Force found insufficient evidence to judge the balance of benefits and harms of screening community-dwelling older adults without recognized signs or symptoms for cognitive impairment. That statement does not apply to evaluating a person who has symptoms.[18]

A test can become more accurate at identifying pathology and still leave the hardest personal question unanswered: what will happen, when, and what difference an intervention would make. Symptomatic diagnostic use does not make asymptomatic screening a cleared route to certainty. It does not retrospectively tell us what Deborah Hall should have done with the bottle she had ordered on Easter Sunday, or what she did.

What it can do is put a boundary around the answer she did not have. The community was right to take her uncertainty seriously, and the intervening studies have made parts of it more measurable. But a measurable marker, an encouraging cognitive score, and a reduced risk of dementia are three different claims. The first list names the conversations supported now at their proper grades. The second names results still worth waiting for, and the null or harmful results that must count just as much when they arrive.

Reference Guide A: Intervention Dossiers

These grades belong to claims, populations, and outcomes, not to an intervention in every setting. The headline asks whether an intervention prevents dementia or slows cognitive decline in at-risk adults without dementia. A stronger result for cognition, a biomarker, or treatment after symptoms begin appears in its own evidence lane.

Evidence-grade summary

The series scale distinguishes the kind of evidence behind each claim. A is a replicated clinical outcome in the relevant population. B is a controlled human signal with limits. B-null is controlled evidence of no effect on the endpoint tested. C is observational or uncontrolled human data. D is preclinical only. E is a forum account or hypothesis. "Insufficient" means nothing fits. Grades attach to the stated claim. "Headline" grades the claim most readers care about: *preventing dementia or slowing cognitive decline in at-risk adults without dementia*. A stronger grade for a narrower claim does not carry over to that headline claim.

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
Blood-pressure control	B. CRHCP dementia RR 0.85 at 4 and 7 yrs; SPRINT MIND (MCI)	White-matter lesion slowing (B)	C, consistent	—	Widely endorsed	B (strongest in book)	Standard care; individual targets set with a clinician
Multidomain lifestyle (FINGER, US POINTER, LatAm-FINGERS)	B, replicated small cognitive gains; no dementia endpoint	—	C	—	Forum favors	B (cognition)	Low risk

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
Speed-of-processing training + boosters (ACTIVE)	B, 20-yr claims-based dementia HR 0.75, one arm only	—	—	—	—	B (narrow)	Low risk; other training types B-null
Aerobic / resistance exercise	B, small executive-function gains	BDNF rises (C)	C for dementia	D (exerkines, GPLD1)	Universal	C for dementia; B for cognition	Low risk; see Book One
HIIT	Insufficient, 5 small inconsistent RCTs	—	—	D	Popular	Insufficient	Cardiac screening where indicated
Hearing correction	B-null overall (ACHIEVE; CHOICE in MCI); B signal in high-risk subgroup	GFAP/NfL lower (C)	C, consistent	—	—	C (B-null primary)	Low risk
Cataract surgery / vision correction	—	—	C	—	—	C	WHO 2026: insufficient to recommend for dementia
Statins / LDL lowering	B-null for the dementia-inclusive composite (STAREE, HR 0.94)	—	C (Lancet LDL factor)	—	Common	B-null in healthy ≥70; C elsewhere	Strong cardiovascular benefit; no cognitive harm
ApoB	—	—	C (Mendelian randomization, mixed)	—	Forum interest	Insufficient	Cardiovascular marker
Lp(a)	—	—	C-null (two large 2025–26 analyses)	—	Forum interest	Insufficient	Cardiovascular marker; no approved Lp(a) drug for dementia

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
PCSK9 inhibitors	Stroke reduction; dementia not affected (meta-analysis)	—	—	—	—	Insufficient	Reassuring cognitive safety
Glucose control / diabetes care	—	—	C (BMJ 2026 cohort)	—	—	C	Standard care
Metformin (non-diabetic prevention)	B-null for overall cognition in DPPOS; dementia signal in a preprint	—	C in T2D	D	Forum staple	C	Rx drug; Book Two covers exercise interaction
SGLT2 inhibitors	—	—	C (cohorts)	—	—	C	Rx for diabetes, heart, kidney
Intranasal insulin	B-null (SNIFF)	—	—	D	Some forum use	B-null	Not approved for cognition
GLP-1 drugs (semaglutide etc.)	B-null in early AD (evoke/evoke+)	Small CSF shifts (B)	C mixed (UK emulation null)	D	Intense	Insufficient for prevention; B-null for treatment	Not approved for AD; see Book Four
Ketogenic diet	B, small, short RCTs in MCI/AD	Ketone PET uptake (B)	—	D	Active threads	C	Lipid rises in some; supervision for diabetes drugs
MCT oil / ketone esters	B, small pooled effect (SMD 0.15 in MCI/AD)	Brain BHB rises (B)	—	D	Active threads	C	GI effects; product claims unregulated

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
MIND diet	B-null (NEJM 2023, vs calorie-restricted control)	—	C	—	Popular	C	Low risk
Mediterranean / plant-based patterns	—	—	C	—	—	C	Low risk
Time-restricted eating / fasting	—	—	—	D	Popular	Insufficient	Caution in diabetes and frailty
Sleep apnea treatment (CPAP)	Insufficient (12-month RCT, small)	—	C	—	—	C	Treat for its own sake
Orexin antagonists (suvorexant)	—	Short-term amyloid/tau changes (B)	—	D	Some forum interest	Insufficient	Rx hypnotic; not approved for prevention
Glymphatic "enhancement"	—	Imaging only (C)	—	D	Hype	Insufficient	—
Menopausal hormone therapy	B-null early start (KEEPS); B harm when started ≥65 (WHIMS)	—	C mixed; meta-analysis null	D	Debated	B-null	2026 FDA label change is not efficacy evidence
Testosterone (men)	B-null (TRAVERSE cognitive substudy)	—	C (biased meta-analysis)	—	Forum use	B-null	Rx for diagnosed hypogonadism; see Book Four
APOE4-specific lifestyle tailoring	B, genotype modifies lifestyle response (pooled 2026)	—	C	D	DrFraser thread	C	Counseling advised before testing

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
APOE gene therapy	—	—	—	D (program paused 2026)	—	Insufficient	Investigational
Bredesen / ReCODE	B-null on MoCA in a non-peer-reviewed 2026 preprint	—	C (case series)	—	Strong testimony (E)	C at best	Costly; supplement burden; Alzheimer Society of Canada criticism
Anti-amyloid antibodies (early symptomatic AD)	A for slowing decline (lecanemab, donanemab)	Amyloid clearance (A)	—	—	—	Insufficient for prevention (trials pending)	Boxed ARIA warning; APOE4 homozygotes highest risk
Trontinemab / other pipeline antibodies	Phase 3 pending (2028)	Amyloid clearance 92% at 28 wks (C, open-label)	—	—	—	Insufficient	Investigational
Blarcamesine	EMA refusal; application withdrawn	—	—	—	Forum interest	Insufficient	Not approved anywhere
p-tau217 blood tests	Diagnostic accuracy validated in symptomatic patients	Predicts 10-yr impairment in healthy adults (C)	—	—	Frequent questions	n/a (diagnostic)	Cleared for symptomatic adults only; not for screening
40 Hz gamma stimulation	B. OVERTURE (76 pts, 6 months); HOPE pending	EEG and atrophy signals (B)	—	D	Some DIY use	B (treatment, small); Insufficient for prevention	Investigational device
Transcranial photobiomodulation	B, one 80-person home RCT in MCI (2026)	—	—	D	DIY interest	C	Consumer devices unregulated for cognition

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
Lithium (low-dose / orotate)	B-null (LATTICE)	—	C (water, cohorts)	D (Nature 2025)	Strong 2025 surge	C	Renal and thyroid monitoring; orotate unproven as distinct
Shingles vaccine	—	—	C (natural experiments: strong design, debated size)	—	Forum interest	C (high-quality C)	Recommended for older adults on its own merits
RSV / flu vaccines	—	—	C	—	—	C / Insufficient	Recommended on own merits
Valacyclovir (HSV)	B-null with harm signal (VALAD)	No biomarker benefit	C (HSV association)	D	Forum interest	B-null (symptomatic AD)	Rx antiviral; not for cognition
NR / NMN (NAD+ precursors)	B-null for cognition (small MCI RCTs); B-null in Parkinson's (NOPARK)	Blood NAD+ rises (B)	—	D	Very active	Insufficient	NMN lawful as supplement (FDA 2025)
NAD+ IV infusions	—	—	—	—	Clinic testimony (E)	Insufficient / E	FDA warning letter (2026): low BP, shaking
GlyNAC	— (AD RCT due 2027)	Glutathione markers (C, pilot abstracts)	—	D	Forum interest	Insufficient	NAC is a drug-supplement hybrid; low acute risk
Creatine	—	Brain creatine +11% (C)	—	D	Rising interest	C	Low risk in healthy kidneys

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
Omega-3 (DHA/EPA)	B-null across RCTs and meta-analyses	CSF DHA engaged (B)	C	D	Common	B-null	Low risk; bleeding caution at high intake
B vitamins (high homocysteine)	B. VITACOG atrophy and cognition signals, small	Atrophy slowing (B)	C	—	Forum interest	C/B in high-homocysteine subgroups only	Low risk
Multivitamin (COSMOS)	B, small cognitive benefit, pooled	—	—	—	—	B (cognition), Insufficient for dementia	Low risk
Cocoa flavanols	B-null primary (COSMOS)	—	—	—	—	B-null	Low risk
Vitamin D	B-null (VITAL)	—	C	—	Common	B-null in replete adults	Correct deficiency for its own sake
Semax / Selank	B for post-stroke recovery (Russian studies, quality concerns)	—	—	D	Peptide thread	Insufficient	Not FDA-approved; PCACvote non-binding
Cerebrolysin	B for post-stroke arm function (CARS); B-null mortality (Cochrane)	—	—	D	Peptide thread	Insufficient	Not FDA-approved; import alerts
Dihexa / P21	—	—	—	D	Hype	D	Research chemicals only
BPC-157 (CNS claims)	— (3 human studies, 30 people, non-brain)	—	—	D	Hype	D/E	No lawful compounding basis as of Oct 2026

Intervention	Human RCT outcome	Biomarker / surrogate	Observational	Animal	Forum / anecdote	Headline	Safety and legal note
Rapamycin / sirolimus	REACH pending; ERAP uncontrolled	CBF rise in APOE4 carriers (C)	—	D	Central to forum	C/D	Boxed warning; off-label; see Book Two
Maraviroc	B-null (A5324, HIV population)	—	—	D	Forum experiment	D	Rx antiretroviral
ARBs (telmisartan)	—	—	C	D	Debated	C	Rx antihypertensive
Bumetanide	—	—	C (EHR)	D	Forum interest	C	Rx diuretic
Melatonin (high dose)	—	—	—	D	Megadose saga (E)	Insufficient	Unregulated doses
Taurine	—	—	C mixed	D	Walked back	Insufficient	—

Blood-pressure control

Claim. Treating uncontrolled hypertension lowers dementia incidence. Evidence lanes. In a cluster-randomized trial involving 33,995 adults across 326 rural Chinese villages, the dementia risk ratio was 0.85 after 48 months. A seven-year conference follow-up reported an adjusted risk ratio of 0.85; it is a later report from the same trial, not an independent replication.[1,2] Grade. B, the strongest headline grade in this guide. Safety. Lower pressure is not an unlimited good: treatment decisions must account for tolerability and other medical conditions. Legal status. Hypertension treatment is standard medical care, not an Alzheimer's drug indication. Pending. Further trials can clarify how well the dementia finding transfers across populations and treatment systems. Sources.[1,2]

Multidomain lifestyle programs

Claim. Coordinated changes in activity, diet, cognitive engagement, and vascular-risk care preserve cognition. Evidence lanes. FINGER found a better cognitive composite after two years than general health advice. US POINTER enrolled 2,111 at-risk adults aged 60–79; both groups improved, but structured support produced a small additional global-cognition gain. LatAm-FINGERS also reported a two-year cognitive advantage over flexible advice. None established reduced dementia incidence.[3,4,5] Grade. B for cognition, not an A-grade prevention result. Safety. The constituent behaviors are generally low risk, though a coordinated program takes time and support. Legal status. No drug approval is involved. Pending. Longer follow-up must test whether small score differences become differences in diagnosed dementia. Sources.[3,4,5]

Speed-of-processing training

Claim. One form of cognitive training may lower later dementia diagnoses. Evidence lanes. The ACTIVE speed-training arm, with booster training, produced a narrow signal in a twenty-year claims-based analysis; the other training arms did not show the same result. A claim recorded in administrative data is not the same measurement as a blinded clinical dementia assessment. Grade. B, narrowly for the tested speed-training approach; other training types have B-null judgments for their tested claims. Safety. Physical risk is low; the principal risk is selling a general prevention promise on the strength of one arm. Legal status. Training is not a medicine. Pending. Independent replication with adjudicated clinical outcomes would make the finding more secure. Sources.

Aerobic and resistance exercise; HIIT

Claim. Regular exercise supports brain function; HIIT is sometimes claimed to do more. Evidence lanes. A randomized-trial meta-analysis in cognitively healthy adults aged 60 or older found small executive-function effects for aerobic and resistance exercise, with reported effect sizes of 0.130 and 0.232. A review of five HIIT trials found no consistent overall-cognition benefit.[6,7] Exercise-related BDNF changes in people with MCI remain surrogate findings. A proposed liver-to-brain factor improved memory-related outcomes in mice, but human studies found no consistent exercise-related change in that factor.[8,9,10] Grade. Exercise: C for dementia, B for cognition; HIIT: Insufficient. Safety. Capacity and cardiac concerns matter more for intense exercise. Legal status. Neither is a drug. Pending. Dementia endpoints remain distinct from fitness and laboratory markers. Sources.[6,7,8,9,10]

Hearing correction

Claim. Correcting hearing loss prevents cognitive decline or dementia. Evidence lanes. Observational studies favor hearing-aid use, including a seven-year emulation estimating dementia risks of 5.0% with a prescription strategy and 7.5% without one; residual confounding remains possible.[11,12] In the randomized CHOICE trial, 703 adults with MCI and moderate-to-severe hearing loss were assigned to intervention or hearing-care education. Dementia-level impairment at 24 months was 3.09% versus 4.74%, a difference that was not statistically significant.[13] Grade. C headline, with B-null overall randomized results and a narrower high-risk signal. Safety. Correction can matter for communication irrespective of dementia. Legal status. Established hearing care. Pending. Longer randomized follow-up may resolve subgroup uncertainty. Sources.[11,12,13]

Vision correction and cataract surgery

Claim. Restoring vision reduces dementia risk. Evidence lanes. A review combining sensory-impairment studies found visual impairment associated with dementia, but mixed observational designs cannot establish what happens after correction.[14] In its 2026 risk-reduction guideline, WHO found the vision-intervention evidence insufficient to recommend correction specifically for dementia prevention; the cataract-surgery evidence it reviewed was observational and of very low certainty for that outcome.[15] Grade. C for the observed association, not a controlled prevention effect. Safety. The ordinary benefits and risks of eye care stand on their own. Legal status. Established clinical care. Pending. Better comparisons must separate improved sight, better cognitive-test performance, and changed dementia incidence. Sources.[14,15]

Statins and LDL lowering

Claim. Lowering LDL prevents dementia as well as cardiovascular events. Evidence lanes. STAREE randomized 9,971 adults aged 70 or older without cardiovascular disease, diabetes, or dementia and followed them for a median 5.9 years. Its composite of death, dementia, or persistent disability did not differ significantly; major cardiovascular events were lower in the statin group. The composite result alone does not establish a standalone dementia effect.[16] The 2024 Lancet Commission included high LDL among modeled modifiable dementia risk factors, which is a different kind of evidence.[17] Grade. B-null for the tested composite in healthy adults 70 or older, without a standalone dementia finding; C for broader dementia-risk associations. Safety. Cardiovascular benefit must not be erased by a neutral composite finding. Legal status. Prescription drugs used within their approved cardiovascular indications. Pending. Longer dementia-specific outcomes remain informative. Sources.[16,17]

ApoB, Lp(a), and PCSK9 inhibitors

Claim. Finer lipid markers or deeper lipid lowering reveal a brain-protection strategy. Evidence lanes. A UK Biobank analysis of 308,019 participants found an ApoB–Alzheimer's association that changed direction after adjustment for APOE ε4, illustrating model dependence rather than a treatment effect.[18] Across 22 randomized PCSK9-targeted-therapy trials involving 64,116 participants, stroke was less frequent, while the dementia estimate had very wide confidence intervals and was not significant.[19] Observational Lp(a) analyses have also yielded null findings; they do not test whether lowering Lp(a) prevents dementia. Grade. ApoB and Lp(a): Insufficient as prevention targets; PCSK9 inhibitors: Insufficient for dementia despite the stroke finding. Safety. Cardiovascular indications are separate. Legal status. PCSK9 drugs are prescription treatments, not approved dementia preventives. Pending. Dedicated cognitive follow-up could narrow uncertainty. Sources.[18,19]

Glucose control and diabetes care

Claim. Better metabolic care reduces dementia incidence in people with diabetes. Evidence lanes. An English cohort of 249,958 adults with type 2 diabetes recorded 22,492 dementia cases over 1,257,998 person-years. Associations involving glucose and HbA1c varied by follow-up period, with nonlinearity and possible reverse causation in shorter follow-up.[20] Such findings describe risk patterns; they do not establish that pushing a particular laboratory value lower will prevent dementia. Grade. C for the brain-specific claim. Safety. Diabetes treatment has benefits and harms independent of speculative dementia effects. Legal status. Established medical care within each treatment's label. Pending. Comparisons that account for disease severity and changes over time would sharpen causal interpretation. Sources.[20]

Metformin

Claim. Metformin prevents dementia, including in people without diabetes. Evidence lanes. A 2026 DPP/DPPOS preprint assessed cognitive-impairment syndromes in 1,483 participants. Original metformin assignment was associated with lower odds of dementia, but the overall distribution of impairment syndromes did not differ significantly, and dementia case numbers were limited.[21] Cohort comparisons in type 2 diabetes provide a separate C lane, susceptible to differences in who receives each drug.[22] Grade. C headline for the observational evidence; the overall randomized cognitive comparison was null, and prevention in healthy non-diabetic adults remains unestablished. Safety. Gastrointestinal effects, kidney-related restrictions, and possible attenuation of some exercise adaptations belong to its benefit–risk assessment.[23,24,25] Legal status. Prescription diabetes drug; prevention is not a labeled indication. Pending. As of October 2026, TAME had not launched and MET-FINGER had no posted results.[26,27] Sources.[21,22,23,24,25,26,27]

SGLT2 inhibitors

Claim. Diabetes drugs in this class lower dementia incidence. Evidence lanes. In a South Korean matched cohort, SGLT2 users had lower recorded dementia risk than thiazolidinedione users, but matching was limited primarily to sex.[28] A separate US electronic-health-record comparison associated metformin plus an SGLT2 inhibitor with lower vascular-dementia incidence, but not with every measured cognitive outcome; its authors warned against causal interpretation.[22] Grade. C. Two associations do not become a randomized prevention trial, and comparator selection can strongly influence results. Safety. Their established diabetes, heart, and kidney uses have their own eligibility and adverse-effect considerations. Legal status. Prescription drugs for labeled indications, not dementia prevention. Pending. Brain-outcome trials or stronger active-comparator analyses are needed. Sources.[22,28]

Intranasal insulin

Claim. Delivering insulin to the brain improves cognition without relying on ordinary blood-glucose treatment. Evidence lanes. In SNIFF, 289 adults with MCI or mild Alzheimer's dementia were randomized to intranasal insulin or placebo for 12 months. The first delivery device proved unreliable; among the 240 participants in the primary, second-device population, cognitive change did not differ between groups.[29] A plausible connection between insulin signaling and Alzheimer's biology cannot substitute for an outcome. Grade. B-null for the tested cognitive claim, not a verdict on every insulin-related mechanism. Safety. An experimental brain-directed intervention should not be treated as interchangeable with prescribed diabetes care. Legal status. Not approved for cognition. Pending. Any new claim requires a defined population, clinical endpoint, and adequately controlled trial. Sources.[29]

GLP-1 drugs

Claim. A metabolic drug class prevents Alzheimer's disease or slows it after symptoms begin. Evidence lanes. Two phase 3 semaglutide trials enrolled 3,808 people with amyloid-confirmed early symptomatic Alzheimer's disease. Semaglutide did not significantly slow decline on the primary CDR-SB endpoint at 104 weeks.[30] In a UK cohort of older adults with type 2 diabetes, GLP-1 initiation was not associated with lower dementia risk than DPP-4 initiation in the intention-to-treat analysis; an as-treated association is more vulnerable to confounding.[31] Grade. Insufficient for prevention, B-null for the tested treatment claim. Safety. Approved indications have their own labels and risk profiles. Legal status. As of October 2026, no GLP-1 drug was approved for Alzheimer's disease or dementia.[32] Pending. ISAP tests tau change in 58 amyloid-positive adults without dementia; PROTECT-Cog has announced a longer multidomain study. Neither has reported efficacy.[33,34] Sources.[30,31,32,33,34]

Ketogenic diet and fasting

Claim. Changing fuel availability slows cognitive deterioration. Evidence lanes. A six-month trial randomized 60 people with early-to-mid-stage Alzheimer's disease to a plant-rich ketogenic diet combined with intermittent fasting or standard care. Mean MMSE change favored the combined intervention, but its design cannot assign the difference to ketosis or fasting individually.[35] Small symptomatic studies and metabolic imaging provide narrower support, not prevention evidence in healthy at-risk adults.[36] Grade. Ketogenic diet: C headline, despite controlled signals in symptomatic populations; fasting alone: Insufficient. Safety. Lipid changes, frailty, and interactions with diabetes treatment complicate broad claims. Legal status. Dietary patterns are not approved Alzheimer's treatments. Pending. Trials separating the components and measuring durable clinical outcomes would address the central ambiguity. Sources.[35,36]

MCT oil and exogenous ketones

Claim. Supplemental ketones provide an alternative brain fuel and improve cognition. Evidence lanes. A 2026 review pooled 38 studies with 1,602 participants; its overall cognitive effect favored ketones, but heterogeneity was high. The MCI/Alzheimer's subgroup estimate was modest, and long-term evidence was limited.[37] A 30-person MCI pilot found greater PET-measured ketone uptake with a combination containing ketones and an NAD+ precursor; it cannot isolate the ketone component.[36] A separate completed study in 99 cognitively intact older adults measured brain metabolism over 28 days, not Alzheimer's efficacy.[38] Grade. C headline, with B in small, narrower cognitive and surrogate lanes. Safety. Gastrointestinal effects and variable product claims matter. Legal status. Products are not approved dementia treatments. Pending. Larger isolated-intervention trials must test meaningful function. Sources.[36,37,38]

MIND, Mediterranean, and plant-based diets

Claim. Food-pattern quality changes long-term dementia risk. Evidence lanes. In a three-year randomized trial of 604 cognitively unimpaired older adults, MIND did not outperform a control diet that also involved mild calorie restriction on global cognition.[39] Long cohorts associate greater Mediterranean and MIND adherence with lower dementia incidence, while a multiethnic cohort found differing associations for healthful and unhealthful plant-based scores. These comparisons cannot remove all differences between the people eating each way.[40,41] Brain-structure associations add a surrogate rather than clinical proof.[42] Grade. MIND: C headline with a B-null randomized comparison; Mediterranean and plant-based patterns: C. Safety. Broad food patterns are generally low risk, but labels alone say little about nutritional quality. Legal status. No drug claim. Pending. Longer controlled follow-up may distinguish diets from supportive study participation. Sources.[39,40,41,42]

Sleep apnea treatment

Claim. Treating obstructive sleep apnea prevents later dementia. Evidence lanes. A randomized study assigned 148 cognitively normal adults with sleep apnea to CPAP plus supportive care or supportive care alone; 124 completed 12 months. It assessed cognition and imaging but did not establish dementia prevention.[43] In a matched Danish registry comparison, dementia and Alzheimer's risk estimates for people with apnea both had confidence intervals crossing no difference. Treatment-related subgroup findings were observational.[44] Grade. C headline, while the available randomized prevention evidence is insufficient. Safety. Sleep apnea has reasons for treatment apart from a brain-prevention claim. Legal status. CPAP is established care for its clinical indication. Pending. Dementia outcomes require longer and better-separated treatment comparisons. Sources.[43,44]

Orexin antagonists and glymphatic claims

Claim. Changing sleep architecture or clearance physiology removes Alzheimer's-related proteins. Evidence lanes. Short-term protein-marker observations attached to suvorexant are a surrogate lane, not evidence of prevented impairment. As of October 2026, the registered SToP-AD study planned to compare suvorexant with placebo in people with poor sleep and measure amyloid-related change; its record did not report efficacy.[45] A separate sleep protocol plans to test increased slow-wave activity and memory-related measures, likewise without results.[46] Grade. Orexin antagonists: Insufficient for prevention; proposed glymphatic "enhancement": Insufficient, despite imaging and animal work. Safety. Hypnotic effects and next-day impairment cannot be ignored because a biomarker hypothesis sounds attractive. Legal status. Suvorexant is a prescription hypnotic, not an approved preventive. Pending. Clinical outcomes must follow credible target engagement. Sources.[45,46]

Menopausal hormone therapy

Claim. Hormone replacement, especially near menopause, protects against dementia. Evidence lanes. Controlled findings include neutral cognition in an early-start setting and a harm signal when treatment began at older ages; those are different populations, not results to average into an endorsement. A 2025 review encompassing one randomized and nine observational studies found no significant association with incident MCI or dementia and concluded that menopausal hormone therapy should not be prescribed for dementia prevention.[47] An autopsy-based cohort reported less Alzheimer's pathology among estrogen-only users but could not establish causality.[48] Grade. B-null headline, with a separate older-start harm signal. Safety. Formulation and clinical context affect risk. Legal status. FDA's 2026 removal of specified boxed-warning statements was a labeling action, not proof of brain benefit.[49] Pending. Better-defined timing studies cannot erase existing controlled findings. Sources.[47,48,49]

Testosterone

Claim. Correcting low testosterone improves memory or prevents dementia in men. Evidence lanes. A larger controlled cognitive substudy found no benefit, supporting a B-null judgment. A meta-analysis of smaller studies in men with hypogonadism reported favorable pooled cognitive estimates but detected publication bias; those findings do not outweigh the larger neutral result.[50] Grade. B-null for the brain claim. Safety. Potential noncognitive benefits and risks belong to assessment of diagnosed hypogonadism, not a dementia-prevention theory. Legal status. Prescription treatment remains bounded by its approved indication; the evidence here does not support prescribing it for prevention. Pending. Further trials would need prespecified, durable cognitive outcomes rather than selective favorable tests. Sources.[50]

APOE4-specific lifestyle tailoring and gene therapy

Claim. Genetic risk identifies either a better lifestyle response or a molecular target. Evidence lanes. A 2026 analysis harmonized three multidomain randomized trials in adults aged 60–85. APOE4 status modified the global-cognition response at 12 months, while the interaction at 24 months was borderline; neither analysis tested dementia incidence.[51] The distinct gene-therapy proposal remained preclinical when its developer paused the program in 2026.[52] Grade. Lifestyle tailoring: C headline with a B genotype-interaction lane; gene therapy: Insufficient. Safety. Genetic information can carry psychological and insurance consequences; GINA does not cover life, disability, or long-term-care insurance. Legal status. Gene therapy is investigational. Pending. Reproducible clinical interactions and human gene-therapy outcomes are separate questions. Sources.[51,52]

Bredesen and ReCODE

Claim. A personalized collection of tests, lifestyle changes, and supplements reverses Alzheimer's disease. Evidence lanes. The original report described ten people without a control group. A later report described seven selected cases and explicitly lacked a denominator, making the proportion who improved unknowable.[53,54] A non-peer-reviewed 2026 preprint also reported a null MoCA finding; that narrower result does not establish whether the larger reversal claim is true. Grade. C at best for uncontrolled human observations. Safety. Complex programs can impose financial and supplement burdens. The Alzheimer Society of Canada distinguishes potentially useful everyday changes from an unproved promise of reversal.[55] Legal status. A branded protocol is not an approved Alzheimer's treatment. Pending. Controlled, independently assessable outcomes would have to test the package without selecting only successes. Sources.[53,54,55]

Anti-amyloid antibodies

Claim. Removing amyloid slows early symptomatic Alzheimer's disease and might eventually prevent symptoms. Evidence lanes. Lecanemab and donanemab have A evidence for slowing clinical decline in appropriately selected people who already have early symptomatic disease. Evidence for prevention in people without symptoms remains Insufficient. Safety. Both carry boxed warnings for amyloid-related imaging abnormalities. A 2026 review reports substantially higher edema-related event proportions among APOE ε4 homozygotes than noncarriers in central-trial settings.[56] Legal status. As of October 2026, both were approved for early symptomatic Alzheimer's disease with confirmed amyloid, not for prevention before symptoms.[57,58,59] Pending. Prevention trials must establish whether any benefit outweighs risks in a population that has no symptoms to treat. Sources.[56,57,58,59]

Pipeline antibodies and blarcamesine

Claim. Newer antibodies or non-amyloid drugs may improve on current symptomatic treatment. Evidence lanes. Trontinemab has shown an open-label amyloid-clearance signal, with phase 3 clinical outcomes pending; amyloid removal alone cannot establish preserved cognition. Blarcamesine has faced regulatory failure and a withdrawn application, not a positive prevention result. Grade. Insufficient for both headline claims. Safety. An investigational product's risks cannot be assumed to match those of an approved member of a broad treatment category. Legal status. As of October 2026, neither was an approved Alzheimer's preventive, and blarcamesine was not approved anywhere. Pending. Prespecified clinical outcomes, not preliminary clearance or expectation, settle the treatment question. Sources.

p-tau217 blood tests

Claim. A blood result can reveal Alzheimer's disease early enough to support prevention decisions. Evidence lanes. Diagnostic performance in symptomatic clinical populations and prediction of future impairment in people without symptoms answer different questions. A test result is not evidence that an intervention works. Grade. Not applicable: this is a diagnostic question, not an efficacy judgment. Safety. An uncertain result can change how a person sees the future without identifying an effective preventive drug. Legal status. As of October 2026, the listed US-cleared Alzheimer blood tests were intended for specified symptomatic adults; none was cleared to screen people without symptoms.[60,61] Pending. Studies must show what screening would change in care and whether those changes improve outcomes. Sources.[60,61]

40 Hz gamma stimulation and photobiomodulation

Claim. Repeated light, sound, or transcranial illumination can slow cognitive loss. Evidence lanes. A small six-month controlled study in 76 patients reported a treatment signal for 40 Hz stimulation. The larger HOPE trial was completed, but as of October 2026 no efficacy results had been posted or announced.[62] A separate 80-person home photobiomodulation trial in MCI does not establish prevention in adults without impairment. Grade. Gamma stimulation: B for the narrow treatment claim, Insufficient for prevention; photobiomodulation: C headline despite its narrow controlled signal. Safety. Consumer equipment and clinical trial devices should not be treated as interchangeable. Legal status. Investigational for these brain claims; consumer cognitive claims lack the assurance of an approved treatment. Pending. Larger trials need durable function and adverse-event outcomes. Sources.[62]

Lithium and lithium orotate

Claim. Restoring low brain lithium prevents Alzheimer's pathology. Evidence lanes. A 2025 study linked lower lithium in human MCI brain tissue with an experimental hypothesis, then reported effects on pathology and memory in mice. It did not test prevention in people.[63,64] Observational human signals and a null controlled treatment finding address different, narrower questions; neither establishes prevention by lithium orotate. Grade. C headline for the observational human evidence; the widely discussed orotate mechanism itself remains preclinical. Safety. Lithium exposure can affect kidneys and thyroid, and an over-the-counter salt is not a clinically validated way to reproduce a mouse experiment. Legal status. Prescription lithium has established psychiatric indications, not dementia prevention. Pending. As of October 2026, a small lithium-orotate feasibility and biomarker-engagement trial in Alzheimer's disease was registered but not yet recruiting.[63,64] Sources.[63,64]

Shingles, RSV, and influenza vaccines

Claim. Preventing certain infections also prevents dementia. Evidence lanes. Shingles-vaccine natural experiments offer a comparatively strong observational signal, although their estimated magnitude is debated. RSV and influenza findings remain observational and less decisive for the brain claim. Grade. Shingles: C; RSV and influenza: C / Insufficient, preserving their separate judgments. Safety. Vaccination decisions have established disease-prevention purposes independent of an uncertain dementia effect. Legal status. Approved vaccines are used within their indications, not as licensed Alzheimer's preventives. Pending. Designs that distinguish vaccination from healthier-user behavior and differences in healthcare access would make the dementia inference firmer. Sources.

Valacyclovir

Claim. Treating herpes simplex infection slows Alzheimer's disease. Evidence lanes. HSV associations and mechanistic proposals led to a controlled test in symptomatic disease. VALAD found no cognitive or biomarker benefit and raised a harm signal. Grade. B-null for the tested symptomatic claim, not proof that every infection-related hypothesis is false. Safety. An antiviral's established uses do not justify exposure for an unproved cognitive purpose. Legal status. Prescription antiviral used for labeled infections, not approved for cognition or dementia prevention. Pending. A different population would require its own controlled rationale and safety case rather than reinterpretation of a null treatment trial. Sources.

NR and NMN

Claim. Raising NAD+ availability preserves cognition. Evidence lanes. Small MCI cognitive trials have been neutral, while blood NAD+ increases remain surrogate findings. In the separate NOPARK trial, 410 people with early Parkinson's disease were randomized for 52 weeks; the clinical difference favored placebo, not NR. Parkinson's disease is not a dementia-prevention population, but the result restrains broad brain-disease claims.[65] Grade. Insufficient headline, with B-null narrow clinical lanes. Safety. A favorable blood marker cannot establish a favorable long-term brain outcome. Legal status. FDA concluded in 2025 that NMN was not excluded from the US dietary-supplement definition under the drug-preclusion provision it addressed; that was not product approval or evidence of efficacy.[66] Pending. Cognition trials must show outcomes beyond biochemical uptake. Sources.[65,66]

NAD+ IV infusions

Claim. Infusions overcome the limitations of oral precursors and improve brain function. Evidence lanes. No published clinical evidence establishes a cognitive or neurodegenerative-disease benefit for NAD+ IV products. An FDA warning letter instead describes a bulk-substance eligibility problem at one outsourcing facility and reports of low blood pressure, shaking, chills, and body aches associated with an NAD+-containing product. It does not measure a risk rate for all infusions.[67] Grade. Insufficient / E; clinic testimony does not constitute an efficacy trial. Safety. Identity, quality, and adverse reactions are material uncertainties. Legal status. The 2026 letter concerns a particular facility; it is neither blanket approval nor a blanket prohibition on every product.[67] Pending. Controlled brain outcomes and independently documented safety would be needed. Sources.[67]

GlyNAC and NAC

Claim. Supporting glutathione synthesis slows cognitive decline. Evidence lanes. An older-adult GlyNAC finding has been reported in a conference abstract, not in a full trial report establishing dementia prevention.[68] A separate 24-week randomized study of 59 adults with possible vascular MCI found no significant additional executive-function benefit from NAC alongside exercise-based cardiac rehabilitation; that was NAC, not GlyNAC.[69] A review found that multi-ingredient Alzheimer's studies cannot isolate NAC's contribution and that most included studies had substantial bias concerns.[70] Grade. GlyNAC: Insufficient; the narrow NAC comparison is null. Safety. Supplement familiarity does not settle prolonged-use benefit–risk questions. Legal status. NAC occupies both drug and supplement contexts; neither establishes dementia efficacy. Pending. An Alzheimer's GlyNAC study had no posted results at its September 2026 registry update.[71] Sources.[68,69,70,71]

Creatine

Claim. Improving brain energy availability preserves thinking. Evidence lanes. An uncontrolled human study reported an 11% increase in brain creatine. Preclinical work offers a rationale, but no completed dementia-prevention outcome trial has shown that the biochemical change preserves cognition. Grade. C for the uncontrolled human finding; the measured change must not be read as an established reduction in dementia incidence. Safety. A low-risk assessment in people with healthy kidneys cannot be generalized to every medical condition. Legal status. A supplement, not an approved Alzheimer's preventive. Pending. Trials need to determine whether altered brain creatine translates into sustained cognition, and in whom. Sources.

Omega-3 fatty acids

Claim. DHA or EPA supplementation prevents cognitive decline. Evidence lanes. A 24-month randomized DHA trial enrolled 365 adults aged 55–80 without dementia who had low dietary DHA and at least one dementia risk factor. DHA changed a CSF fatty-acid measure, but cognition and brain volume did not differ between groups; dropout reached 38%.[72] That is target engagement without a demonstrated clinical benefit. Grade. B-null headline across the clinical trial evidence, with B for the biochemical surrogate. Safety. Bleeding concerns at high intake and the reason for taking a product belong in the assessment. Legal status. Supplements are not approved dementia preventives. Pending. Longer studies might refine subgroup questions, but a changed CSF measure cannot itself overrule a null cognitive result. Sources.[72]

B vitamins, multivitamins, cocoa, and vitamin D

Claim. Common supplements offer inexpensive brain protection. Evidence lanes. The findings differ by product and population: small VITACOG atrophy and cognition signals in high-homocysteine subgroups; a modest controlled cognition signal for the COSMOS multivitamin; a null primary cocoa-flavanol result; and a null vitamin D result in replete adults. Grade. B vitamins: C/B only in the specified subgroup; multivitamin: B for cognition but Insufficient for dementia; cocoa and vitamin D: B-null for their tested claims. Safety. Deficiency correction is a separate medical question from prevention in replete adults. Legal status. Supplement status is not a brain-efficacy endorsement. Pending. Subgroup findings need confirmation without broadening them to everyone. Sources.

Semax, Selank, and cerebrolysin

Claim. Neuroactive peptide products improve brain recovery and might prevent dementia. Evidence lanes. A Semax report in 110 people after ischemic stroke describes better rehabilitation-related outcomes, but does not establish Alzheimer's prevention; no published Selank-specific human efficacy result establishes that claim.[73] In exploratory CARS, cerebrolysin favored arm function after stroke, while a Cochrane review of stroke trials found no probable mortality benefit and a possible increase in nonfatal serious adverse events.[74,75] Grade. Insufficient for the prevention claims, notwithstanding the narrower post-stroke signals. Safety. Uncertain characterization and product quality add to clinical uncertainty. Legal status. None is FDA approved. A July 2026 advisory vote concerning Semax did not confer approval or establish a lawful compounding basis; FDA staff had recommended against its inclusion on the 503A Bulks List.[76,77,78] Pending. Well-controlled, brain-specific human outcomes remain absent. Sources.[73,74,75,76,77,78]

Dihexa and P21

Claim. Experimental compounds that affect neuronal signaling or synapses can restore cognition. Evidence lanes. Support for Dihexa and P21 remains preclinical; no published human cognitive outcome trial establishes a benefit for either. A cellular or animal response does not establish exposure, long-term safety, or function in an aging human brain. Grade. D for each separate claim. Safety. Uncharacterized human risks and uncertain product identity make analogy with approved drugs especially weak. Legal status. Research chemicals, not approved medicines for cognition or dementia. Pending. Before a clinical benefit claim can be assessed, regulated human research must establish basic safety and prespecified outcomes. Sources.

BPC-157

Claim. A peptide associated with tissue-repair claims protects the brain. Evidence lanes. A 2026 review found three small human studies totaling 30 participants, covering nonbrain indications or safety; it rated their certainty very low. None established a cognitive effect.[79] A non-peer-reviewed analysis of a mixed-peptide dataset also found substantial failures against the authors' purity-and-abundance benchmarks, but its findings cannot be converted into a BPC-157-specific contamination rate.[80] Grade. D/E for CNS claims. Safety. Limited human safety evidence and uncertain product characterization remain concerns. Legal status. The July 2026 PCAC recommendation for 503A inclusion was nonbinding, not FDA approval. As of October 2026, FDA had posted no final action adding BPC-157 to the list.[76,77,81] Pending. Regulatory decisions and controlled brain trials are separate unresolved matters. Sources.[76,77,79,80,81]

Rapamycin and sirolimus

Claim. mTOR inhibition preserves brain function before symptoms begin. Evidence lanes. A 23-person uncontrolled pilot reported cerebral-blood-flow increases in APOE4 carriers after sirolimus exposure, without a clinical prevention endpoint. Part I findings from the Missouri study were reported in September 2026; a separate study of asymptomatic APOE4 carriers was recruiting as of October 2026.[82,83] ERAP enrolled 14 people with symptomatic disease, and its results were preprinted rather than posted on the registry.[84] Grade. C/D headline: a human surrogate alongside animal evidence, not demonstrated prevention. Safety. Sirolimus labeling carries boxed immunosuppression, infection, and malignancy warnings.[85] Legal status. Approved for specified nonaging indications; dementia prevention would be off-label and is not supported as a prescribing conclusion here.[85] Pending. As of October 2026, REACH listed 40 enrolled and no posted results.[86] Sources.[82,83,84,85,86]

Maraviroc

Claim. CCR5 blockade improves aging-related memory. Evidence lanes. In the 96-week randomized A5324 trial, 191 people with HIV and neurocognitive impairment improved similarly whether or not their treatment was intensified with maraviroc and dolutegravir. Mouse work found that altering CCR5 signaling restored memory linking in aged animals; neither result establishes a healthy-aging benefit in humans.[87,88] Grade. D for aging-related memory, with a separate B-null lane in the HIV population. Safety. An approved antiretroviral has clinically significant warnings and interaction considerations that cannot be set aside for a speculative brain use. Legal status. Prescription HIV treatment, not an approved dementia preventive; off-label use would be a clinician question, not an inference from this evidence. Pending. As of October 2026, MARCH and CAMAROS both had unknown registry status and no posted results.[89,90] Sources.[87,88,89,90]

Telmisartan and other ARBs

Claim. One blood-pressure drug class, and perhaps particular agents within it, protects the brain beyond pressure control. Evidence lanes. An observational comparison favored ARBs over another antihypertensive class for dementia outcomes. Such comparisons remain vulnerable to differences in patients, achieved pressure, and prescribing decisions. Grade. C for the ARB dementia association; choosing telmisartan specifically for prevention remains an unproved narrower claim. Safety. Excess pressure lowering and kidney or potassium effects can matter even if a mechanistic brain story is appealing. Legal status. Prescription antihypertensives used for labeled indications, not approved as Alzheimer's preventives. Pending. A recruiting telmisartan arm in a Parkinson's platform trial concerns another disease and does not resolve dementia prevention.[91] Sources.[91]

Bumetanide

Claim. A loop diuretic can counter APOE4-related Alzheimer's biology. Evidence lanes. Computational and animal findings have been paired with a retrospective health-record association among people already receiving the drug. That convergence supports investigation but not causal prevention. Grade. C headline for the observational lane, rather than a controlled human outcome. Safety. Volume depletion, low pressure, kidney effects, and electrolyte disturbances weigh differently when the proposed benefit is unproved. Legal status. Prescription diuretic for its established indications, not an approved dementia treatment or preventive. Pending. A controlled brain-outcome study would have to separate any drug effect from the medical reasons people received it. Sources.

Melatonin

Claim. High-exposure melatonin protects against neurodegeneration beyond any sleep effect. Evidence lanes. Animal findings and forum testimony have not established a human Alzheimer's prevention outcome. A separate heart-failure association was reported in a conference abstract, with no full peer-reviewed paper available as of October 2026; an association in health records cannot establish that melatonin caused heart failure.[92] Grade. Insufficient. Safety. Larger exposure is not automatically a stronger version of ordinary circadian signaling, and incomplete supplement-use records complicate harm estimates. Legal status. Supplement marketing does not establish an approved dementia indication. Pending. Peer-reviewed assessment of the cardiovascular signal and controlled prevention outcomes would answer different questions; neither has established the brain claim. Sources.[92]

Taurine

Claim. Replacing a presumed age-related taurine deficit preserves cognition. Evidence lanes. Later longitudinal findings have challenged a universal age-related decline, weakening the simple deficiency rationale. Animal longevity findings and heterogeneous human observations do not establish dementia prevention. Grade. Insufficient, rather than a clinical grade inherited from an aging mechanism. Safety. A laboratory concern in a disease model should not be presented as proof of harm in healthy people, just as an animal benefit is not proof of protection. Legal status. Supplement status does not imply cognitive efficacy. Pending. Human trials would need defined baseline status, cognitive endpoints, and safety follow-up before a broad brain claim could be made. Sources.

Reference Guide B: Biomarkers and the Trial Calendar

A biomarker is a location in an argument

A blood result, a brain image, and a change in daily functioning are not three ways of saying the same thing. They occupy different places in an argument about Alzheimer's disease. A blood test may help identify pathology. An image may show that a treatment engaged its intended target. A cognitive or functional outcome asks whether people experienced a benefit. Moving successfully from one place to the next requires evidence, not confidence in the first measurement.

That distinction has become more useful as blood tests have entered clinical evaluation. As of October 2026, FDA-cleared Alzheimer's blood tests in this guide are intended to help assess people with cognitive symptoms; none is cleared to screen people without symptoms. They are not stand-alone diagnoses.[1,2] A person who has noticed persistent cognitive changes and a person who feels well but wants to know her future risk are asking different questions. Accuracy established in the first setting cannot simply be transferred to the second.

The FDA's May 2025 clearance of the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio applies to adults aged 55 or older with signs and symptoms of cognitive decline. In the FDA-reviewed set of 499 plasma samples from cognitively impaired adults, 91.7% of positive results corresponded to amyloid plaques on PET or in cerebrospinal fluid, while 97.3% of negative results corresponded to negative reference findings; fewer than 20% were indeterminate. Those figures describe agreement with pathology testing in the studied clinical population, not the chance that a healthy person with a positive result will develop dementia.[1]

Roche announced FDA clearance of Elecsys pTau217 in August 2026 to aid assessment of people aged 55 or older with signs, symptoms, or complaints of cognitive decline. It reports positive, intermediate, or negative categories. Roche says it has not been established for predicting dementia development or monitoring treatment effects.[2] In a separate analysis of 303 patients with mild cognitive impairment or mild dementia, the Elecsys p-tau217 assay achieved an area under the curve of 0.93 against a

cerebrospinal-fluid reference; under the study's two-threshold approach, 27% of cases landed between the thresholds. That substantial middle category is a reminder that useful diagnostic tests do not always produce a simple answer.[3]

When a biomarker change is large enough to matter

The July guide described several kinds of measurement error: changes between laboratory platforms, specimen handling, scanner settings, image-processing methods, and the effects of repeatedly taking a cognitive test. They matter most when a small change is being asked to carry a large conclusion. An apparent improvement in a blood marker might exceed ordinary analytical variation yet still have no demonstrated relationship to preserved memory. Conversely, a worrying result might call for clinical interpretation without establishing that decline is inevitable.

The blood amyloid-beta 42:40 ratio and phosphorylated tau 217 address related but distinct features of Alzheimer's pathology. The ratio helps account for differences in overall amyloid-peptide production; p-tau217 reflects a tau response associated with Alzheimer's-related pathology. Neither is a cognitive score, and a percentage change in either cannot be read as the same percentage change in dementia risk. Assay platform, specimen handling, kidney function, and clinical setting can affect interpretation. That is why comparison with PET or cerebrospinal-fluid findings is valuable in a diagnostic study, and why diagnostic agreement does not, by itself, establish a prevention strategy.

Other markers answer broader questions. Neurofilament light chain, or NfL, can signal neuroaxonal injury from more than one cause. Glial fibrillary acidic protein, or GFAP, reflects astrocytic processes but does not measure memory directly. Total tau in cerebrospinal fluid can signal injury without identifying its cause on its own. If these markers move during a small treatment study, the movement deserves attention. It does not automatically tell us whether the treatment helped, harmed, or coincided with another biological change.

Imaging carries similar boundaries. FDG-PET estimates patterns of regional glucose uptake; arterial-spin-labeling MRI estimates cerebral blood flow; volumetric MRI estimates the size of brain structures. Acquisition conditions and analysis choices can affect all three. A pre/post increase in blood flow, or a short-interval change in hippocampal volume, is not an image of neurons being saved. Without a concurrent control

group, even a carefully measured change remains vulnerable to ordinary variation and to mistaken assumptions about what would otherwise have happened.

Nor can a test result be interpreted apart from the people tested. Some direct-to-consumer services offer Alzheimer's blood biomarkers, while specialists have warned that results may reach consumers without the cognitive evaluation and clinical context needed to interpret them.[4,5] Research in people without symptoms can estimate future risk, but a positive biomarker is not a guarantee of future impairment.[5] The U.S. Preventive Services Task Force found insufficient evidence to assess the balance of benefits and harms of screening community-dwelling adults 65 or older for cognitive impairment when they have no recognized signs or symptoms. That statement concerns screening, not the evaluation of a person with symptoms.[6]

A research predictor and a cleared screening test therefore solve different problems. Prediction asks whether groups with different results have different rates of later impairment. Screening asks whether testing people who feel well, followed by whatever happens next, produces more benefit than harm. It also has to contend with indeterminate findings, false alarms, follow-up testing, and the prospect of learning a risk for which no proven prevention treatment follows. As of October 2026, no drug or supplement is approved to prevent Alzheimer's disease in people without symptoms.

How to read a registry record

The other kind of uncertainty in this guide concerns time. A trial registry is a public account of a study's design and reported progress, not an appointment for its findings to arrive. Its *primary completion* date marks final collection of data for the primary outcome; *study completion* includes final data collection more broadly. Neither promises a press release, a posted results entry, or a peer-reviewed paper. Estimated dates may change, and a record may remain stale after an estimate has passed.

The endpoint matters as much as the date. A trial measuring time until clinical progression can address a different question from one measuring amyloid clearance. A trial in mild-to-moderate Alzheimer's disease cannot establish prevention in people who have no symptoms, however compelling its mechanistic findings appear. Similarly, a registry listing for an FDA-regulated device study does not establish that the device is approved for marketing or that it works.[7,8]

This is particularly relevant to antibodies. In 1,169 cognitively unimpaired adults with elevated brain amyloid, the A4 trial found that solanezumab did not slow cognitive decline over 240 weeks. The drug did not substantially clear plaque, so the result does not settle every question about earlier amyloid removal, but it rules out claiming success for the treatment tested.[9] In early *symptomatic* Alzheimer's disease, lecanemab and donanemab slowed decline in their respective trials, while producing clinically significant amyloid-related imaging abnormalities. Those treatment findings cannot be reassigned to symptom-free adults.[10,11]

As of October 2026, lecanemab and donanemab are treatments for eligible patients with early symptomatic Alzheimer's disease, not approvals for asymptomatic prevention. The U.S. Approval of a subcutaneous lecanemab product for starting treatment as well as maintenance does not change that population boundary. Donanemab's label carries a boxed warning that amyloid-related imaging abnormalities can be fatal and that risk is higher in APOE4 homozygotes.[12,13] The point of prevention trials is to test whether a benefit exists on the other side of that boundary, against risks incurred by people who may never have developed symptoms.

Trial-watch cards, status checked October 9, 2026

The calendar below is a reading aid, not a forecast of positive findings. "Expected" means a dated possibility reported in a publication or a date recorded for data collection. An empty stretch is not evidence that research stopped: several relevant studies have no announced readout date. An ongoing study should not acquire a year merely because a calendar looks incomplete.



Figure 14. The trial calendar from late 2026 to 2031. The dates are registry estimates as of October 2026 and will move. The table that follows gives each readout and its source.

Expected	Readout	Affects	Registry/source
Late 2026, conditional	TRAILBLAZER-ALZ 3 could read out in 2026 if enough events accrue; no finding is implied by that possibility.	Whether donanemab delays progression in a preclinical population; not a result as of this guide.	2026 pipeline review[14]
Late 2026 onward; no dated efficacy release established	HOPE's registry reports primary completion on June 22, 2026, and study completion on August 17, 2026. As of October 2026, no topline efficacy results had been posted or announced.	Clinical effects of 40 Hz light-and-sound stimulation in mild-to-moderate Alzheimer's disease, not prevention.	HOPE registry[8]
June 30, 2028 registry primary completion	The CMS national anti-amyloid antibody registry lists this date for primary completion, not publication.	Evidence gathered under Medicare's coverage-with-evidence-development arrangement.	CMS registry NCT06058234[15]

Expected	Readout	Affects	Registry/source
2028 reported primary completion	TRONTIER 1 and 2 are ongoing; their clinical outcomes have not been reported.	Whether trontinemab benefits people with early symptomatic disease.	Reported trial timing[16,17]
No established readout date	EJS ACT-PD is recruiting; arm-specific findings have not been reported.	A telmisartan-related neurodegeneration question in Parkinson's disease, not a direct test of Alzheimer's prevention.	ClinicalTrials.gov NCT07207057[18]

Several studies belong beside that calendar precisely because a primary-completion date is not a readout date. MET-FINGER, combining a lifestyle intervention with metformin, remained active without posted results as of October 2026; its registry estimated primary completion on June 30, 2028.[19] An Alzheimer's GlyNAC randomized trial has been discussed, but no dated, trial-specific readout is established here. AHEAD 3-45 is part of the prevention discussion, but it has neither a reported efficacy result nor an established readout date here.

HOPE illustrates why completion deserves its own wording. The central study randomized roughly 670 people with mild-to-moderate Alzheimer's disease to a light-and-sound intervention or sham comparison, with a combined cognitive and daily-function primary endpoint. The registry listed the study as completed when rechecked on October 10, 2026; no topline efficacy result had been posted there or announced by the company as of that date.[8] Earlier EEG findings were presented as supportive mechanistic evidence, while exploratory cerebrospinal-fluid protein changes came from an analysis of 10 participants in another study. Neither substitutes for HOPE's clinical outcome.[20,21]

The device category also needs separation by condition and timescale. A randomized trial recruited 80 people with mild cognitive impairment due to Alzheimer's disease and found better cognitive test scores after 12 weeks of home-based transcranial photobiomodulation than after placebo treatment. It was short and did not establish dementia prevention.[22] A network meta-analysis reported favorable cognitive-scale estimates for photobiomodulation across varied studies, but differences among devices and study methods prevent treating that pooled number as the expected result of one consumer product.[23]

In the antibody pipeline, TRAILRUNNER-ALZ 3 is testing remternetug against placebo in preclinical Alzheimer's disease and mild cognitive impairment, with time to clinical progression as its primary endpoint. The cited conference abstract describes the study, not an efficacy finding, and supplies no readout date for this calendar.[7] Roche has also described a planned PrevenTRON study in cognitively unimpaired people at high risk of progression. Its reported trontinemab amyloid-clearance figures came from an open-label extension; plaque reduction there does not establish preserved cognition, much less prevention.[16,17]

A long pipeline can make every pending study feel like confirmation waiting to be published. The January 1, 2026 pipeline snapshot counted 192 trials assessing 158 drugs, including 54 phase 3 trials. Those are counts of questions being asked, not answers.[14] A calendar should preserve that distinction even when a date approaches: first check what was actually measured, in whom, and against what comparison; then check whether results have appeared. A missed estimate is a reason to verify the record, not evidence for or against the intervention.

A final rule for every marker and registry

The common error in biomarkers and trial calendars is to fill the gap between an observation and a hoped-for outcome with an assumption. A pathology marker can improve a symptomatic diagnostic assessment without becoming a test that should be offered to everyone. A treatment can clear amyloid without having shown that it prevents dementia. A completed study can remain an unanswered question until its clinical outcomes are available.[1,2,8,16,17]

The useful record is therefore a modest one: what population was studied, what the test or trial was designed to answer, what result has actually been reported, and which date still needs verification. Those details do not make uncertainty disappear. They keep a reader from mistaking an early signal, or a square on a calendar, for a life already protected.

Reference Guide C: Three Worksheets

A claim about protecting the brain can change meaning as it passes from a study title to a conversation. “Improved a cognitive score” becomes “prevents dementia.” “Detected a biomarker” becomes “predicts my future.” These three worksheets are meant to preserve the distinctions that disappear in that passage. They are records of evidence and uncertainty, not plans for testing or treatment.

An earlier collection offered ten worksheets; this guide keeps three: a claim card, a blood-test disclosure preparation sheet, and a trial-watch ledger. The other seven have been retired. Readers seeking a fuller method for assessing studies or preparing for a clinical discussion can turn to Book One’s *Source Appraisal* and *Clinician Conversation* handbooks. Each sheet asks for the same seven anchors: a claim, population, endpoint, citation, grade, date checked, and a finding that could upgrade or downgrade the assessment. Repeating those fields makes it harder to mistake a change in wording for a change in evidence.

Claim Card

The claim card catches an idea before its edges blur. Write one proposition, not a verdict on an intervention. “This improves brain health” leaves too much unstated: whose brain, which measure, compared with what, and over what period? A claim about cognition in people who already have mild impairment is not the same claim as dementia prevention in people without symptoms. Nor does a change in a blood or imaging marker establish that daily function will change.

The grade belongs to the *written claim*. On the series scale, A denotes a replicated clinical outcome in the relevant population; B, a controlled human signal with limits; B-null, controlled evidence of no effect on the endpoint tested; C, observational or uncontrolled human data; D, preclinical data; and E, an account or hypothesis. “Insufficient” is appropriate when none fits. A narrower claim may earn a stronger grade than the prevention headline. A null finding should remain attached to the endpoint and population actually tested, rather than becoming a pronouncement that every related idea has failed.

Claim: In _____, _____ changes _____ compared with _____ over _____.

Population: _____ Endpoint: _____

Citation and study type: _____ Grade for this exact claim: _____

Date checked: _____

Possible upgrade: A study finding that would strengthen this claim: _____

Possible downgrade: A result, limitation, or harm that would weaken it: _____

Consider the difference between two possible cards for multidomain lifestyle programs. A card about cognitive scores in at-risk older adults can draw on randomized trials; a card asserting that the programs prevent dementia cannot borrow that grade when dementia incidence was not the endpoint. A pooled analysis of three completed lifestyle trials also reported that APOE4 status modified the intervention effect on global cognitive scores at 12 months; the 24-month interaction was borderline. It did not establish reduced dementia incidence.[1] The first finding may sharpen a question about who responds on a measured score. It does not fill in the missing clinical event.

A card can also prevent a biomarker result from carrying more weight than it earned. In a randomized, 24-month DHA trial involving 365 adults aged 55–80 without dementia, a CSF biochemical measure changed, but cognition and brain volumes showed no observed treatment difference.[2] Those findings belong on the same card. Omitting either one makes the account less useful: the biochemical result indicates an effect on the measured marker, while the clinical and imaging results limit what can be claimed from it.

An upgrade should name evidence that could actually answer the question, such as a replicated trial measuring the stated outcome in the stated population. A downgrade might be a well-conducted null trial, a failure to replicate, substantial attrition, or evidence that an apparent association depended on a biased comparison. Neither field asks the reader to predict the future. It records, in advance, what would make a revision intellectually honest.

Blood-Test Disclosure Preparation

A blood-test result can arrive before its meaning is settled in the reader's mind. This sheet is for preparing questions about *disclosure and interpretation*, not for deciding whether to seek a test or for interpreting a result alone. It separates three issues often compressed into one: what an assay measures, whether its evidence applies to the person being tested, and what receiving the information might mean beyond medical care.

As of October 2026, FDA-cleared Alzheimer's blood tests described in this guide aid evaluation of adults with cognitive symptoms or complaints; none is cleared to screen people without symptoms. The Lumipulse ratio test and Elecsys pTau217 are not stand-alone diagnoses.[3,4] Accuracy measured among people undergoing evaluation for cognitive problems should not simply be transferred to a population without symptoms. The FDA-reviewed Lumipulse sample consisted of cognitively impaired adults, and a separate Elecsys p-tau217 analysis studied patients with mild cognitive impairment or mild dementia.[3,5] A positive biomarker result is not a guarantee that symptoms will develop.[6]

Claim the test result is being asked to support: _____

Population for whom the test was studied or cleared: _____

Endpoint measured or predicted, and the endpoint I am asking about: _____

Citation: _____ *Grade for the stated claim:* _____

Date checked: _____

What information would upgrade this interpretation? _____

What finding or mismatch would downgrade it? _____

Disclosure questions to take to a clinician: Who receives the result? How will an indeterminate result be explained? What clinical information would be considered alongside it? What records might retain it? _____

The two endpoint blanks matter. A test that helps assess amyloid pathology during a clinical evaluation is not thereby shown to prevent dementia, or even to predict an individual's course precisely. Roche states that Elecsys pTau217 has not been established for predicting dementia development or monitoring treatment effects.[4] Direct-to-consumer offerings create another

potential mismatch: availability outside a conventional clinical visit does not provide the cognitive evaluation needed to place a result in context.[6,7]

Disclosure also has a nonmedical dimension. The Genetic Information Nondiscrimination Act, or GINA, prohibits genetic discrimination in health insurance and in employment by employers with at least 15 employees. GINA does not cover life insurance, disability insurance, or long-term-care insurance.[8] Those boundaries should not be reduced to "genetic information is protected." They are especially relevant when a discussion of a blood biomarker expands to APOE testing or family risk. This sheet cannot resolve insurance or legal questions; it gives the reader a place to record them before disclosure, rather than after an unexpected result.

Trial-Watch Ledger

A trial-watch ledger prevents an anticipated result from quietly becoming an established one. It also preserves negative findings. A registry entry, conference presentation, preprint, peer-reviewed report, and independent replication are different stages of evidence. Recording the stage beside the claim makes a headline easier to assess months later, when a projected completion date may have passed but results have not appeared.

Claim being watched: _____

Study population and comparator: _____

Primary endpoint and follow-up period: _____

Citation or registry identifier; current reporting stage: _____

Grade for the claim today: _____ *Date checked:* _____

Possible upgrade: What reported result or replication would strengthen it? _____

Possible downgrade: What null result, safety finding, revision, or missing report would weaken it? _____

Change since last check, including "no reported result": _____

For a ledger entry, "results pending" is not a favorable outcome. The entry should preserve what was actually registered as the primary endpoint, whether the reported population matches the prevention claim, and whether a later analysis is exploratory. A positive marker can be worth

watching without being promoted to a clinical result. Conversely, a null primary outcome should not vanish because a secondary measure attracted attention.

The ledger is also where dates earn their keep. A citation identifies the document behind the current wording; the date checked shows when that document's status was last reviewed. If a paper replaces a preprint, record the replacement rather than layering its findings onto the old version. If no result appears, write that plainly instead of inferring success or failure. These small habits make later revisions traceable.

Used together, the sheets leave three distinct records: what the claim says, what a potentially consequential test result can and cannot disclose, and what a future trial would need to report before the claim changes. Their value is not that they settle uncertain questions. It is that they keep an answer from becoming stronger merely because it has been repeated.

Reference Guide D: Three Evidence Files

A claim can be biologically plausible, supported by a real study, and still answer the wrong question. These three files begin with proposals that attracted attention in longevity discussions: slowing brain aging with rapamycin, protecting cognition through vascular care, and preventing dementia through shingles vaccination. They differ in an important respect. One rests largely on mechanism and early human signals; one includes randomized dementia outcomes in people with uncontrolled hypertension; and one draws on an unusually informative natural experiment that remains observational. The task in each case is to name the comparator, the outcome measured, the inference permitted, the safety boundary, and the next test.

Evidence File 1: Rapamycin and prevention

Rapamycin's appeal begins with mTOR, a pathway involved in growth and cellular maintenance. Animal and mechanistic work supplies reasons to investigate whether changing that pathway could affect processes implicated in Alzheimer's disease. It does not establish that a cognitively healthy person who uses sirolimus will be less likely to develop dementia. Animal models cannot reproduce the full mixture of vascular injury, other pathology, comorbidity, and medication exposure seen in late-life human disease.

The prevention question is demanding: in adults without cognitive symptoms but at elevated risk, does assignment to sirolimus rather than placebo reduce subsequent cognitive decline or dementia, with harms measured for long enough to judge the tradeoff? Risk definition matters. So do disease stage and the distinction between a scan that changes and a person whose cognition or function is preserved. A study in people who already have mild cognitive impairment can inform this question without answering it.

As of October 2026, the REACH registry lists a placebo-controlled rapamycin trial in people with amnestic mild cognitive impairment or early Alzheimer's disease as active but not recruiting. It records 40 participants, a March 2026 primary completion date, and no posted results. A

completion date is not a finding; nor would a finding in early symptomatic disease automatically establish prevention before symptoms. REACH's comparator is nonetheless an advance over an uncontrolled series: randomization can help separate drug effects from expectation, natural variation, and repeated-testing effects.

ERAP offers a more cautionary early-human example. In its completed single-arm, open-label study, 14 people enrolled and 13 completed; the prespecified FDG-PET measure did not change in the reported brain regions. Results appeared in a preprint, but no results were posted on the trial registry as of October 2026.[1] With no concurrent control group, even a favorable scan change would have been hard to attribute to treatment; an unchanged prespecified measure provides no positive clinical-prevention result.

The Missouri program asked a narrower imaging question. Its peer-reviewed September 2026 report described an open-label pilot of 23 adults aged 45–65. Cerebral blood flow rose in several measured regions among the nine APOE ε4 carriers, with no significant change among the 14 non-carriers. There was no control group and no dementia-prevention endpoint. A randomized comparison in women who carry APOE ε4 is registered, but its existence is a proposal for a stronger test, not confirmation of the pilot signal.

Cerebral blood flow is worth measuring, yet it is sensitive to physiology and measurement conditions. More flow in a region need not mean less Alzheimer pathology, fewer symptoms, or better function years later. An uncontrolled subgroup contrast is especially vulnerable to chance and selection. These limitations do not make the pilot worthless; they define its proper use as a source of hypotheses for the registered comparison, not a result to generalize to all at-risk adults.

Stage further complicates the claim. A drug could affect maintenance, immune activity, or neuronal function differently before and after disease becomes apparent. A stage-dependent rapamycin report remained a conference abstract as of October 2026, so it cautions against assuming that "earlier" must be better; it does not establish the best treatment window. Prevention also exposes people who may never develop dementia. That raises the standard for acceptable harm even when early imaging looks encouraging.

As of October 2026, sirolimus is approved in the United States for specified medical indications, not for aging or dementia prevention. Its labeling

carries a boxed warning concerning immunosuppression, infection, and malignancy; using it for longevity is off-label. Established uses do not transfer their benefit-risk balance to people seeking to prevent an uncertain future illness. Any off-label question belongs with a clinician, and the evidence here does not support prescribing sirolimus for dementia prevention.

The next decisive test would assign a clearly defined at-risk population to drug or control, specify clinical outcomes in advance, measure exposure and relevant biology, and capture adverse events and missing data over adequate follow-up. Replication would matter, particularly if the first positive result came from a subgroup or surrogate endpoint. Until then, the headline prevention claim remains early-stage: controlled clinical evidence is pending, while the current human signal is principally an uncontrolled imaging observation.

As of October 2026, REACH was active but not recruiting, with 40 participants enrolled and no results posted.[2] ERAP had completed enrollment of 14 participants; summary results were posted in the EU clinical-trials register and the main report remained a preprint, with no results on ClinicalTrials.gov.[1] The University of Missouri reported findings from the first part of its ApoE-dependent cerebral blood-flow study in *Journal of Cerebral Blood Flow & Metabolism* in September 2026, while its registry had no posted results.[3] None of these records establishes that rapamycin prevents dementia.

Evidence File 2: Vascular protection and brain aging

Vascular protection starts from a different position. Hypertension is an established clinical problem, and a trial can ask directly whether improving its control changes later dementia diagnoses. That question should not be blurred into a claim that one favored antihypertensive molecule has a special anti-Alzheimer effect. The first tests a treatment strategy against usual care; the second requires a comparison among drugs or strategies that controls blood pressure comparably.

The China Rural Hypertension Control Program, or CRHCP, randomized 326 rural villages comprising 33,995 adults aged 40 or older with uncontrolled hypertension. Its village-doctor-led intensive-control intervention was compared with usual care. At 48 months, the all-cause dementia risk ratio was 0.85, with a 95% confidence interval of 0.76–0.95;

serious adverse events were fewer in the intervention group. This is a clinical dementia endpoint, not merely an imaging or laboratory signal.[4]

A seven-year conference report described dementia in 8.85% of the intervention group and 10.55% of the usual-care group, with an adjusted risk ratio of 0.85. It follows the same randomized program, rather than supplying an independent replication, and its publication stage differs from the peer-reviewed 48-month report.[4,5] Longer follow-up makes the persistence of an effect more informative, but it does not remove questions about how completely outcomes were captured or how well the intervention transfers to other health systems.

SPRINT MIND tests a related strategy without providing the same dementia finding. Among 9,361 adults with hypertension, probable dementia occurred at 7.2 versus 8.6 cases per 1,000 person-years under intensive versus standard blood-pressure control. The hazard ratio, 0.83, had a 95% confidence interval of 0.67–1.04: the probable-dementia result was not statistically significant. Mild cognitive impairment *was* reduced (hazard ratio 0.81), as was the combined mild-cognitive-impairment-or-dementia endpoint (0.85). The trial stopped early for cardiovascular benefit.[6] Thus CRHCP's dementia outcome and SPRINT MIND's clearer MCI signal support a serious vascular-prevention hypothesis without becoming two identical positive dementia trials.

The comparator is central to applying these results. CRHCP compared organized intensive control with usual care in people whose hypertension was uncontrolled. It did not compare two agents at the same achieved pressure, and it did not enroll normotensive adults to test medication solely for brain protection. A favorable outcome from better care cannot be assigned to an angiotensin receptor blocker, much less to one proposed "brain-penetrant" ARB. Observational comparisons of individual agents remain vulnerable to differences in why clinicians prescribed them, treatment changes, and patients' underlying health.

Lipids illustrate another tempting transfer of evidence. STAREE randomized 9,971 community-dwelling adults aged 70 or older without cardiovascular disease, diabetes, or dementia to atorvastatin or placebo and followed them for a median 5.9 years. Its composite of death, dementia, or persistent physical disability did not differ significantly (hazard ratio 0.94; 95% confidence interval 0.84–1.05), although major cardiovascular events were lower with atorvastatin (hazard ratio 0.70). The reported composite cannot establish a standalone dementia-prevention

benefit.[7] Calling this a vascular benefit is justified; treating that benefit as proof of cognitive protection is not.

There is a second limit to the STAREE comparison: a result in relatively healthy adults aged 70 or older is not a verdict on every lipid-lowering decision in people with different cardiovascular risks. Nor does the trial turn blood-pressure control into an LDL-lowering intervention. It shows why related endpoints, cardiovascular events, MCI, dementia, and disability-free survival, must retain their separate names when results are summarized.[6,7]

Even biomarker associations can shift with the analysis. In a UK Biobank study of 308,019 participants, the ApoB association with Alzheimer's disease was not evident in the main analysis; after adjustment for APOE ε4 allele count, its direction was inverse. Neither model demonstrates that changing ApoB changes dementia risk.[8] In a meta-analysis of 22 randomized PCSK9-targeted therapy trials involving 64,116 participants, stroke estimates favored treatment, while dementia-event estimates were too imprecise to establish a benefit or settle the question confidently.[9] Those findings are relevant to vascular health and cognitive safety, but they do not provide an agent-specific dementia-prevention strategy.

The safety boundary follows the population. In people with hypertension, sustained pressure control is ordinary care, while treatment choices also have to account for tolerability and potential harms. In someone without that indication, adding a prescription drug for speculative neuroprotection presents a different balance. The unresolved question is not simply "does vascular health matter?" CRHCP has measured a dementia outcome for an intensive-care strategy. The narrower next test would compare appropriate antihypertensive strategies at similar achieved pressures, with prespecified cognitive or dementia outcomes and adequate harm assessment. That is what a claim of special brain protection by a particular agent would require.

Evidence File 3: Shingles vaccination and the Welsh natural experiment

The shingles-vaccine claim has an unusually sharp comparison, although no one was randomized by researchers. Wales used a date-of-birth cutoff to determine eligibility for a live-attenuated zoster vaccine. People born just on opposite sides of the cutoff could be similar in age yet face very different opportunities to be vaccinated. In the primary analysis of 282,541 people without dementia at baseline, vaccination uptake was 47.2% among those just eligible and 0.01% among those just ineligible.[10]

The question is whether that eligibility-driven difference led to fewer *new dementia diagnoses*, not whether vaccination altered an Alzheimer biomarker. Over seven years, the Welsh analysis estimated that vaccine receipt was associated with a 3.5-percentage-point lower probability of a new dementia diagnosis, corresponding to a 20.0% relative reduction; its 95% confidence interval for the relative reduction was 6.5–33.4%. The estimated effect was stronger among women. This was a natural experiment, not a randomized trial.[10]

The cutoff helps with one of observational research's hardest problems. A straightforward comparison between people who choose vaccination and people who do not can capture differences in health, access to care, or willingness to seek preventive services. Birth-date eligibility creates a strong change in uptake that is less directly tied to those choices. Still, the inference depends on whether other relevant circumstances also changed at the cutoff and on how faithfully recorded diagnoses represent underlying disease. The numerical estimate should not be read as a guaranteed benefit for every vaccinated person.

An Australian quasi-experiment offers a useful comparison without being an exact replication of the Welsh estimate. Using an age-based cutoff for access to the live vaccine, it found that *eligibility* was associated with a 1.8-percentage-point decrease in new dementia diagnoses over 7.4 years. That is an eligibility effect, not an estimate based on confirmed vaccine receipt; its outcome analysis included 18,402 people.[11] The distinction matters when comparing effect sizes across studies: eligibility can change vaccination without making everyone eligible a vaccine recipient.

There is also a temporal challenge. An August 2026 commentary argued that very large effects implied by some zoster-vaccine natural experiments are hard to reconcile with a true effect on all-cause dementia and may be partly inflated by bias. It noted that shingles and dementia declines in

Wales appeared concurrently, rather than shingles reduction clearly preceding the dementia decline.[12] That observation does not erase the eligibility contrast. It asks whether the proposed causal story fits the timing, and whether ascertainment or other pathways could account for some of the measured difference.

The product boundary is just as important. The Welsh and Australian cutoff studies concern a live-attenuated vaccine; they do not establish the dementia effect of recombinant Shingrix.[10,11] An electronic-health-record comparison reported 18% more dementia-diagnosis-free time over 18 months among recombinant shingles-vaccine recipients than among influenza-vaccine recipients. That is a different observational comparator, a different follow-up period, and not a randomized dementia-prevention test.[13] It cannot simply be substituted for seven-year evidence from a birth-date cutoff.

As of October 2026, Shingrix is recommended for eligible older adults for shingles prevention, not indicated as a dementia-prevention treatment.[14] Its established purpose stands independently of the dementia hypothesis. The safety and policy boundary is therefore not to make an unproved cognitive promise part of the indication. Nor should results from one vaccine formulation be presented as the measured effect of another.

A persuasive next test would examine dementia outcomes after recombinant vaccination using a comparison that resists differences in health-care use and diagnosis, with enough follow-up to assess timing and enough detail to distinguish vaccine receipt from mere eligibility. Independent analyses of birth-date cutoffs should probe what else changed at those thresholds and whether diagnosis patterns explain part of the association. The Welsh result earns a high-quality observational grade for the claim it measured. It does not yet earn the grade of a randomized clinical dementia outcome.

What the three files reveal

The distance between a result and a prevention claim differs across the files. Rapamycin has a plausible target and early human observations but lacks a reported controlled prevention outcome. CRHCP measured dementia diagnoses in a randomized hypertension-care strategy, while SPRINT MIND's statistically clearer finding was MCI rather than probable dementia. The Welsh cutoff produces a strong observational contrast for the live shingles vaccine, but its effect size and transfer to recombinant vaccination remain open to challenge.[4,6,10,12]

These differences are more useful than a single label such as "promising." A comparator says what was actually tested. An endpoint says whether investigators measured biology, cognition, diagnosis, or another health outcome. A safety boundary asks who would bear harm while benefit remains uncertain. And a well-specified next study shows what could change the assessment. None of that requires dismissing an intriguing result. It requires keeping the result attached to its population, design, date, and limits.

Glossary

Absolute risk. The probability that an event will occur in a defined population over a stated period. It shows the scale of an outcome that a relative effect alone cannot convey.

Adverse event. An unfavorable medical occurrence during a study, whether or not the intervention caused it. A *serious* adverse event meets criteria such as death, life threat, hospitalization, or disability.

All-cause dementia. An outcome combining dementia diagnoses from different causes. It captures more events than an Alzheimer's-specific outcome but cannot establish an effect on Alzheimer's disease itself.

Amyloid beta. Peptides derived from amyloid precursor protein. Some forms aggregate into plaques, a feature of Alzheimer's pathology. Amyloid is central to several diagnostic and drug-development approaches, but it does not explain the entire disease.

ApoB. Apolipoprotein B, the principal protein on atherogenic lipoprotein particles. A blood measurement of ApoB approximates the number of those particles; it is distinct from APOE genotype.

APOE. The gene encoding apolipoprotein E. Its ε4 allele raises the risk of late-onset Alzheimer's disease but neither guarantees disease nor accounts for every case. APOE also participates in lipid transport and other biological processes.

ARIA-E. Amyloid-related imaging abnormalities with edema or effusion: MRI findings of swelling or fluid leakage associated with some anti-amyloid antibodies. ARIA-E may be symptom-free or clinically significant.

ARIA-H. Amyloid-related imaging abnormalities with hemorrhage, including small brain bleeds and superficial siderosis seen on MRI. ARIA-H and ARIA-E can occur together; their risks and interpretation depend on clinical context.

Association. A statistical relationship between variables. It may reflect causation, reverse causation, confounding, selection, measurement error, or chance.

Attributable fraction. An estimate of the proportion of cases in a population statistically attributable to an exposure under specified causal assumptions. Estimates for several risk factors cannot simply be added because exposures overlap.

Autophagy. Cellular processes that deliver material to lysosomes for degradation and recycling. Increasing an autophagy marker in a model does not establish that an intervention improves human health.

B-null. A classification used in some Alzheimer's biomarker frameworks when the measured "B," or biofluid tau, component is negative by that framework's criteria. Its meaning depends on the assay and classification scheme; it is not a declaration that disease is absent.

BDNF. Brain-derived neurotrophic factor, a signaling protein involved in neuronal survival and plasticity. Blood BDNF measurements do not straightforwardly represent concentrations or effects within the brain.

Biomarker. A measurable indicator of a biological process, disease process, or response to an intervention. A useful diagnostic or monitoring biomarker is not automatically a validated substitute for a clinical outcome.

Blood–brain barrier. The cells, junctions, and transport systems that regulate exchange between blood and the central nervous system. Barrier changes may accompany aging, vascular injury, inflammation, and neurodegeneration.

Causal inference. The use of study design, data, and explicit assumptions to estimate whether changing an exposure would change an outcome. Even sophisticated observational methods cannot remove bias from factors that remain unmeasured.

CCR5. C-C chemokine receptor type 5, involved in immune signaling. Experimental findings concerning neural plasticity have prompted research on CCR5 antagonism, without establishing a dementia benefit.

CDR-SB. Clinical Dementia Rating–Sum of Boxes, a clinician-rated measure combining cognitive and functional domains. It is used in Alzheimer's trials; a difference between groups requires interpretation alongside its size, uncertainty, and harms.

Cerebral blood flow. Blood delivery to brain tissue. Imaging methods can estimate perfusion, but a change in measured flow is not, by itself, evidence of improved cognition.

Clinical endpoint. An outcome concerning how a person feels, functions, or survives. Cognitive and everyday-function measures are generally closer to patient benefit than a change on a scan or laboratory test.

Clinical significance. The practical importance of a finding, distinct from whether a statistical test crosses a chosen threshold. A precisely estimated effect can still be too small to matter much.

Cluster randomization. Assignment of groups—such as clinics or communities—rather than individuals to study conditions. Analysis must account for similarities among people within each cluster.

Cognition. Mental functions including memory, attention, language, processing speed, and executive function. A combined score may conceal differences among these domains.

Confidence interval. A range produced by a statistical method that reflects uncertainty under its assumptions. Its width and inclusion of effects that would matter clinically deserve more attention than a simple "significant" label.

Confounding. Distortion arising when another factor influences both an exposure and an outcome. Statistical adjustment helps only when relevant confounders are adequately measured and modeled.

Coverage with evidence development. A coverage arrangement that links payment for a service to participation in specified evidence collection.

Coverage conditions, eligible services, and research requirements are policy-specific and should be verified for the period in question.

Cox model. A common model for time-to-event data that estimates hazard ratios. Its interpretation depends in part on assumptions about how hazards compare over time.

Dementia. A syndrome in which cognitive decline interferes with independent function. Alzheimer's disease is one possible cause; vascular, Lewy body, frontotemporal, and mixed causes also occur.

Effect modification. A difference in an exposure's effect across groups, such as disease stages or genotypes. A plausible subgroup finding remains uncertain when it is small, unplanned, or unreplicated.

Endpoint multiplicity. The increased opportunity for apparently positive results when researchers test many outcomes, time points, subgroups, or analyses. Prespecification and appropriate statistical controls help limit misleading findings.

Exerkine. A signaling molecule whose release or activity changes with exercise and may contribute to effects in other tissues. The label covers diverse molecules and does not establish that reproducing one signal reproduces exercise's effects.

External validity. The extent to which a study's findings apply beyond the people and conditions studied. A sound result in one disease stage or care setting may not transfer to another.

503A bulks list. A federal regulatory framework concerning bulk drug substances that may be used in compounding under Section 503A, subject to applicable conditions. A substance's status, including any interim policy, requires current verification; listing is not FDA approval of a compounded product.

GFAP. Glial fibrillary acidic protein, an astrocyte-associated protein measurable in blood and cerebrospinal fluid. Elevated levels can reflect a glial response but are not specific to Alzheimer's disease.

GINA. The Genetic Information Nondiscrimination Act, a US law that restricts certain uses of genetic information in health insurance and employment. It does not cover life, disability, or long-term-care insurance.

Glymphatic system. A proposed account of fluid and solute exchange involving cerebrospinal fluid, interstitial fluid, perivascular routes, and

supporting cells. How best to measure these processes in living humans—and their causal importance for dementia—remains debated.

GlyNAC. A combination of glycine and N-acetylcysteine studied as precursors for glutathione production. Findings about biochemical markers or small human studies do not establish dementia prevention.

Hazard. The event rate at a particular point among people who have not yet had the event. A hazard ratio does not directly state the absolute number of events prevented.

Heterogeneity. Variation in results across studies or participants. It can arise from real differences in interventions and populations, from study bias, or from chance.

HIS-Q. A questionnaire used to assess perceived health impacts or symptoms in some research settings. Its interpretation depends on the particular instrument, validation population, and outcome being studied; a questionnaire score is not a diagnosis.

Insulin resistance. Reduced responsiveness to insulin in relevant tissues. Peripheral measures do not directly measure brain insulin signaling; "type 3 diabetes" is a research shorthand, not a formal Alzheimer's diagnosis.

Intention-to-treat. Analysis of participants according to their randomized assignment, regardless of subsequent adherence or switching. It generally preserves the comparison created by randomization.

Interaction. A change in one exposure's effect or safety when another drug, condition, genotype, or behavior is present. Interactions may alter drug concentrations or combined biological effects.

Internal validity. The credibility of a study's conclusion for the participants studied. Allocation, masking, retention, measurement, and analysis can all affect it.

Ketone ester. A manufactured compound studied for its ability to raise circulating ketones. A rise in ketones demonstrates a metabolic effect, not a proven cognitive or dementia-prevention benefit.

Lithium orotate. A lithium-containing compound sold as a supplement in some markets. It should not be treated as equivalent to evidence for prescription lithium: formulations, exposures, evidence, and safety oversight differ.

Lp(a). Lipoprotein(a), an inherited lipoprotein-associated cardiovascular risk marker. Its concentration is largely genetically influenced, and laboratory units and assays affect comparisons.

MCT. Medium-chain triglycerides, fats that can be metabolized differently from longer-chain fats and can raise ketone production. Metabolic plausibility does not settle whether an MCT intervention improves meaningful cognitive outcomes.

Mild cognitive impairment. Cognitive decline greater than expected for a person's circumstances that does not substantially eliminate independent function. Causes and trajectories differ; progression to dementia is not inevitable.

Multidomain intervention. A study approach combining components such as physical activity, nutrition, cognitive activities, or vascular-risk management. Even a positive combined result may not reveal which component was responsible.

mTOR. Mechanistic target of rapamycin, a kinase in two major signaling complexes. These regulate processes including growth, nutrient sensing, metabolism, and autophagy; effects differ by tissue and context.

NAD+. Nicotinamide adenine dinucleotide, a molecule involved in cellular energy transfer and other reactions. Changes in NAD-related laboratory measures do not establish clinical benefit from products marketed to raise it.

Natural experiment. A study that uses an exposure difference arising from a policy, event, or other circumstance outside researchers' direct assignment. Causal interpretation still depends on whether the comparison is credible.

Neurofilament light. A neuronal structural protein measurable in blood or cerebrospinal fluid, often abbreviated NfL. Higher levels can indicate neuroaxonal injury but do not identify its cause.

Neurovascular unit. Interacting brain blood vessels, supporting cells, neurons, and surrounding tissue that link activity, blood supply, and barrier function.

NfL. Abbreviation for neurofilament light. It is a broad injury marker, not an Alzheimer's-specific test.

NMN. Nicotinamide mononucleotide, a molecule in pathways that produce NAD+. Evidence that an intervention changes a pathway marker should not be mistaken for evidence that it prevents cognitive decline.

NR. Nicotinamide riboside, another precursor in NAD+ metabolism. Its effects on laboratory measures and its effects on clinical outcomes are separate questions.

Number needed to harm. The inverse of an absolute increase in risk over a stated period. Its value depends on the outcome, population, baseline risk, and follow-up.

Number needed to treat. The inverse of an absolute risk reduction over a stated period. It is incomplete without the outcome, population, and duration.

Observational study. A study in which researchers do not randomly assign the exposure. Such studies can address long-term outcomes and uncommon harms, but causal claims require careful scrutiny.

Open-label study. A study in which participants and investigators know the intervention being received. It can answer some feasibility questions but is vulnerable to expectation and assessment effects.

PACC. Preclinical Alzheimer Cognitive Composite, a combined cognitive measure developed to detect subtle change in people without overt impairment. Its sensitivity does not make every score difference clinically meaningful.

PCAC. A patient-centered advisory committee, or a similarly named advisory group, depending on the program using the abbreviation. Its role and authority must be established from that program’s documents rather than inferred from the acronym.

PCSK9. A protein that affects the removal of LDL particles from blood. PCSK9 is a target of approved lipid-lowering drugs, but effects on cardiovascular risk should not be recast as established dementia prevention.

Perivascular spaces. Spaces around small vessels entering the brain, sometimes visible on MRI. Their appearance may relate to age and small-vessel disease, but methods of measurement and clinical meaning vary.

Pharmacodynamics. What a drug does to the body, including target engagement and downstream biological effects. A measurable effect on a target need not translate into patient benefit.

Pharmacokinetics. What the body does to a drug through absorption, distribution, metabolism, and elimination. Blood exposure and brain exposure are not necessarily the same.

Phosphorylated tau. Tau protein bearing phosphate modifications. Certain measures in cerebrospinal fluid or blood can aid Alzheimer's assessment, depending on the assay and intended use.

Photobiomodulation. Research on biological effects of exposure to particular forms of light. Devices and study conditions differ, and mechanistic findings do not establish dementia treatment or prevention.

Preclinical. Research performed before definitive human clinical testing, often in cells, tissues, or animals. In Alzheimer's research, the word can also describe a disease stage before symptoms; context determines its meaning.

Preprint. A scientific manuscript made public before formal peer review. It allows early scrutiny, but methods, results, and conclusions may change.

Primary outcome. The main outcome designated before a study's results are known. A favorable secondary result does not automatically rescue a negative primary result.

p-tau217. Tau phosphorylated at a particular site and measurable with certain blood or cerebrospinal-fluid assays. It is a promising Alzheimer's biomarker, but accuracy and appropriate use depend on the test and population. No blood test is cleared to screen people without symptoms.

Randomized controlled trial. A study that assigns interventions by chance. Randomization improves baseline comparability on average; attrition, unmasking, and selective analysis can still bias results.

Recombinant zoster vaccine. A non-live vaccine used to prevent shingles. Observational research on vaccination and dementia is of interest, but associations do not by themselves prove dementia prevention.

Regression discontinuity. A causal-inference design comparing people just above and below a threshold that determines exposure. It is strongest when people cannot precisely manipulate which side of the threshold they occupy.

Regression to the mean. The tendency for an unusually high or low measurement to be followed by one closer to average, even without intervention. It can make uncontrolled before-and-after comparisons misleading.

Relative risk. Event probability in one group divided by event probability in another. A large relative difference can represent a small absolute difference when events are rare.

Replication. Testing a finding in new data, preferably independently. Repeating an analysis in the same dataset does not provide the same protection against a misleading result.

Reverse causation. A situation in which an outcome, or its early stages, influences the apparent exposure. Early neurodegenerative changes may alter sleep or activity years before diagnosis.

Slow-wave sleep. A stage of non-REM sleep marked by prominent slow electrical activity. Associations with memory and brain-fluid dynamics do not establish that artificially changing this stage prevents dementia.

Statistical power. The probability of detecting a specified effect if it exists, given a study's assumptions. Low power can make both negative findings and apparently positive estimates harder to interpret.

Surrogate endpoint. A biomarker or intermediate outcome used in place of a clinical outcome. Correlation with disease is insufficient: a valid surrogate must reliably reflect an intervention's effects on benefit and harm in the relevant setting.

Target engagement. Evidence that an intervention reached and affected its intended biological target. It can clarify a trial result but does not establish that patients benefited.

Target-trial emulation. An observational analysis designed around the eligibility, assignment, follow-up, and outcomes of a hypothetical randomized trial. Clear design can reduce some biases, not eliminate unmeasured confounding.

Tau. A protein with normal roles in cells, including association with microtubules. Abnormal forms contribute to neurofibrillary pathology in Alzheimer's disease and other conditions.

Type I error. A false-positive conclusion under a statistical testing framework. Multiple testing and selective reporting can increase the practical risk of one.

Type II error. Failure to detect an effect that exists. A negative result may reflect no effect or limitations in sample size, follow-up, exposure, or measurement.

White-matter hyperintensity. A bright area on certain MRI sequences, often associated with age and cerebral small-vessel disease. It is not specific to one cause.

Z-drug. A nonbenzodiazepine hypnotic class that includes zolpidem. Observational links with dementia are difficult to separate from insomnia, other health conditions, and changes preceding diagnosis.

40 Hz gamma stimulation. Experimental sensory stimulation intended to influence brain activity around 40 cycles per second. Evidence of altered brain signals or biomarkers does not establish meaningful cognitive benefit or dementia prevention.

Notes and Sources

Each numbered note below corresponds to a superscript number in the chapter text. Notes are numbered afresh in each chapter. Published dates are as shown by the publisher; every source was retrieved or rechecked between October 9 and October 10, 2026. PubMed identifiers (PMIDs) were verified against the National Library of Medicine's records on the date of this edition. Forum posts are cited by public handle, post number, thread title, date, and permanent URL; they are testimony, not evidence of efficacy. Material carried from the July 2026 edition that rests on the July archive crawl is listed under that chapter's forum threads.

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- The flagship thread this chapter is built from in its entirety — opened by Deborah_Hall, March 31, 2024; over 1,000 replies and 100,000+ views as of the July 2026 crawl, the single most-read thread in the archive examined for this book.

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- Thread "Low Dose Naltrexone (LDN)" (213 replies) — checked for DrFraser's direct participation and Alzheimer's-relevant content; found neither. Not used.
- Thread "An Expert Consensus Statement: The Essential Biomarkers of Aging" (10 replies) — checked; a real consensus statement, but covers general aging biomarkers (GDF-15, IGF-1) rather than the Alzheimer's-specific markers (p-Tau217, amyloid 42:40) this chapter already covers. Not genuinely additive; not used beyond this note.
- Thread "Glycine+NAC vs Rapamycin" (377 replies, 45,016 views) — sampled for Chapter Three's brief GlyNAC grounding; not used as a standalone chapter or major section, per its own standard of resisting material that doesn't clear a genuine relevance bar.

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A synthesis chapter; draws on sources already listed under Chapters Two through Seven. No new external sources are introduced. Forum material includes Schwartz336's and DrFraser's informal physician-to-physician consultation over a lab result, and CronosTempi's account of discarding an unverifiable imported generic empagliflozin shipment.

Chapter 22: Two Lists: What to Do Now, What to Watch

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